



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 22

A. R. Katritzky &
A. J. Boulton

Advances in
**Heterocyclic
Chemistry**

Volume 22

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

Four chapters in the present volume bring older reviews up to date. Those on the quinoxalines (Cheeseman and Werstiuk) and on heteroaromatic quaternization (Zoltewicz and Deady) carry forward contributions on the same subjects in Volumes 2 (1963) and 3 (1964), respectively, of this Series, while those on the phenanthrolines (L. A. Summers) and the isatogens and indolones (Hiremath and Hooper) deal with topics previously covered elsewhere. The cyclazines, a relatively new field of chemistry, are reviewed by Flitsch and Krämer, and the azapentalenes—the wide variety of nitrogen-containing heterocycles formed by the fusion of two aromatic five-membered rings—are collected into one chapter by Elguero, Claramunt, and A. J. H. Summers.

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The Phenanthrolines

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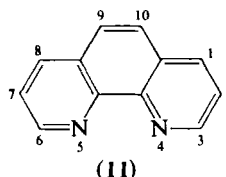
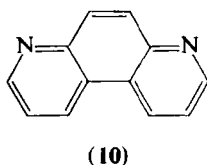
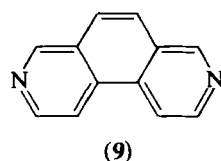
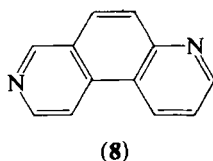
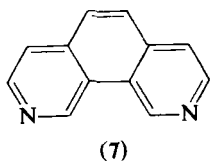
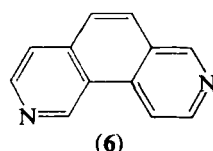
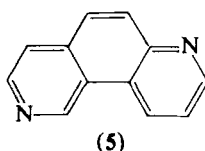
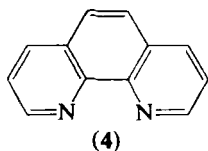
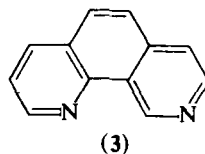
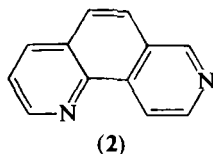
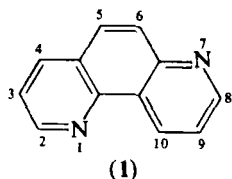
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I. Introduction

Although the term phenanthroline is sometimes considered to include all the isomeric diazaphenanthrenes, it is now usually applied only to those diazaphenanthrenes containing one nitrogen atom in a peripheral position in each of the two outer rings of phenanthrene. This definition of a phenanthroline is in accord with *Chemical Abstracts* nomenclature. There are consequently ten phenanthrolines.

The numbering of the phenanthroline ring system still causes some confusion. The *Chemical Abstracts* numbering, which we adopt throughout this article, is generally preferred, and the ten isomers are then designated as 1,7- (1), 1,8- (2), 1,9- (3), 1,10- (4), 2,7- (5), 2,8-

(6), 2,9- (7), 3,7- (8), 3,8- (9), and 4,7- (10) phenanthrolines. The numbering system based on the phenanthrene ring, however, is still used by some groups, especially in Germany. 1,10-Phenanthroline, for example, is then named as 4,5-phenanthroline (11).



This numbering not recommended;
see structure 1

The most common phenanthrolines, the 1,7-, 1,10-, and 4,7-isomers, are frequently known as *m*-, *o*-, and *p*-phenanthroline, respectively, the nomenclature referring to their original synthesis from the corresponding phenylenediamine.

All the phenanthrolines then known were reviewed by Kermack and McKail¹ (up to about 1954) and the 1,7-, 1,10-, and 4,7- isomers by Graham² (up to 1952). 1,8- and 3,8-Phenanthrolines were included in a review of diazaphenanthrenes by Thirtle³ (up to 1952). A review of the phenanthrolines in Polish⁴ appeared in 1972.

This review covers the chemistry and uses of the phenanthrolines since 1952 and, taken in conjunction with the earlier reviews by Kermack and McKail,¹ Graham,² and Thirtle,³ provides a complete survey of the phenanthrolines to mid-1975. References to work reported in most chemical journals in late 1975 and early 1976 are also included. The review excludes the extensive metal and nonmetal coordination chemistry of 1,10-phenanthroline and its derivatives and the analytical applications of the 1,10-phenanthrolines. For the sake of completeness, sections are included in this article that give references to the review literature on these topics.

Apart from a report⁵ on the isolation of 1,10-phenanthroline from crude oil, the phenanthrolines are not known to occur in nature.

The first phenanthroline to be prepared was 1,7-phenanthroline by Skraup and Vortmann⁶ in 1882, followed one year later by the synthesis of 4,7-phenanthroline.⁷ 2-Methyl-1,10-phenanthroline was the first 1,10-phenanthroline to be reported,⁸ the parent compound being synthesized 9 years later by Blau.⁹ 1,8-Phenanthroline was prepared¹⁰ in 1945. The synthesis of the 3,8-isomer was claimed¹¹ in 1940, but there is doubt about the structure of the product. The remaining isomers, 1,9-, 2,7-, 2,8-, 2,9-, 3,7-, and authentic 3,8-phenanthroline, were not obtained until 1966, when Perkampus and Kassebeer¹² formed all the phenanthrolines by irradiation of appropriate 1,2-di(pyridyl)ethylenes. A derivative of 2,8-phenanthroline had, however, been synthesized 2 years earlier.¹³

¹ W. O. Kermack and J. E. McKail, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, pp. 344–383. Wiley, New York, 1961.

² B. Graham, in "Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings" (C. F. H. Allen, ed.), pp. 386–456. Wiley (Interscience), New York, 1958.

³ J. R. Thirtle, in "Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings" (C. F. H. Allen, ed.), pp. 320–385. Wiley (Interscience), New York, 1958.

⁴ J. Mlochowski and W. Sliwa, *Wiad. Chem.* **26**, 603 (1972).

⁵ D. M. Jewell and G. K. Hartung, *J. Chem. Eng. Data* **9**, 297 (1964).

⁶ Z. H. Skraup and G. Vortmann, *Monatsh. Chem.* **3**, 572 (1882).

⁷ Z. H. Skraup and G. Vortmann, *Monatsh. Chem.* **4**, 570 (1883).

⁸ J. Gerdeissen, *Ber.* **22**, 244 (1889).

⁹ F. Blau, *Monatsh. Chem.* **19**, 666 (1898).

¹⁰ F. Misiani and M. T. Bogert, *J. Org. Chem.* **10**, 347 (1945).

¹¹ P. Ruggli and O. Schetty, *Helv. Chim. Acta* **23**, 725 (1940).

¹² H. H. Perkampus and G. Kassebeer, *Liebigs Ann. Chem.* **696**, 1 (1966).

¹³ K. W. Merz, J. Weidlich, and J. Fink, *Arch. Pharm.* **297**, 392 (1964).

TABLE I
SOME PROPERTIES OF THE PHENANTHROLINES

Phenanthroline	Melting point (°C)	Dipole moment, μ (D)	Dissociation ^a constants	
			pK ₁	pK ₂
1,7-	79 ^b	2.1 ^{16, 17}	4.0 ¹⁹ 4.3 ²⁰	1.0 ¹⁹ 0.75 ²⁰
1,8-	100–104 ¹² 105–108 ¹⁴ 111–115 ¹⁰	3.9 ¹⁷	4.6 ²¹	0.55 ²¹
1,9-	90 ¹² 103–104 ¹⁵	4.2 ¹⁷	4.9 ²¹	0.5 ²¹
1,10-	117 ^{b, c}	4.1 ¹⁸ 3.6 ¹⁶ 3.9 ¹⁷	4.8–5.2 ^b	–1.4 ²⁰ –1.6 ^{23, 24} –1.75 ²¹ –1.8 ²⁵
2,7-	143 ¹² 144–145 ¹⁵	0.15 ¹⁷	4.7 ²¹	1.75 ²¹
2,8-	109–110 ¹²	2.2 ¹⁷	4.7 ²¹	2.2 ²¹
2,9-	141–143 ¹² 144–145 ¹⁵	3.8 ¹⁷	4.8 ²¹	2.3 ²¹
3,7-	115–118 ¹²	2.25 ¹⁷	4.65 ²¹	1.8 ²¹
3,8-	139–141 ¹² 225 ¹¹	0.13 ¹⁷	4.35 ²¹	2.1 ²¹
4,7-	171–177 ^b	3.6 ¹⁶ 3.7 ¹⁷	4.0 ¹⁹ 4.2 ²¹ 4.6 ²²	1.6 ²¹ 1.7 ²²

^a At about 25°C.

^b Various authors.

^c Anhydrous.

¹⁴ R. F. Homer, *J. Chem. Soc.*, 1574 (1958).

¹⁵ S. Hünig, J. Gross, E. F. Lier, and H. Quast, *Liebigs Ann. Chem.*, 339 (1973).

¹⁶ C. W. N. Cumper, R. F. A. Ginman, and A. I. Vogel, *J. Chem. Soc.*, 1188 (1962).

¹⁷ H. H. Perkampus, P. Mueller, and J. Knop, *Z. Naturforsch. B.* **26**, 83 (1971).

¹⁸ P. E. Fielding and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1811 (1951).

¹⁹ P. Krumholz, *J. Am. Chem. Soc.* **73**, 3487 (1951).

²⁰ H. H. Perkampus and H. Kohler, *Z. Elektrochem.* **64**, 365 (1960).

²¹ V. T. Bluhm, H. H. Perkampus and J. V. Knop, *Ber. Bunsenges. Phys. Chem.* **77**, 116 (1973).

²² A. Grabowska, B. Pakula and J. Pancir, *Photochem. Photobiol.* **10**, 415 (1969).

²³ R. H. Linnell and A. Kaczmarczyk, *J. Phys. Chem.* **65**, 1196 (1961).

²⁴ W. A. E. McBryde, *Can. J. Chem.* **43**, 3472 (1965).

²⁵ A. A. Schilt and W. E. Dunbar, *Tetrahedron* **30**, 401 (1974).

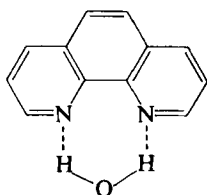
II. Physical Properties

A. CRYSTAL STRUCTURE

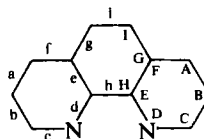
All ten of the parent phenanthrolines are solids (see Table I). Most of the crystal structure work so far reported has been concerned with 1,10-phenanthroline and its derivatives. Crystal structure data and X-ray powder work on 1,10-phenanthroline hydrate²⁶⁻²⁸ confirm, as expected, that it exists as the monomer (12) with hydrogen bonding between the nitrogen atoms and the hydrogens of a water molecule.²⁶ Crystal data on 2,9-dimethyl-1,10-phenanthroline have also been described.²⁹

Although high-resolution X-ray diffraction analysis of the parent 1,10-phenanthroline molecule has not been reported, many papers describing X-ray structure determinations of metal complexes of 1,10-phenanthroline have appeared. These results have been summarized.³⁰ Although in some cases the dimensions of the 1,10-phenanthroline ligand may have been distorted owing to the constricting influence of the binding metal atom, a fairly accurate picture of the bond lengths and angles of the undistorted 1,10-phenanthroline molecule can be obtained from these studies. The structure of the 1:1 complex of 1,10-phenanthroline with 7,7,8,8-tetracyano-*p*-quinodimethane has also been determined.³¹ Typical bond lengths and angles of 1,10-phenanthroline so obtained are compared with those of phenanthrene in Table II.

As in phenanthrene,³² bond *i* in 1,10-phenanthroline (13) is much shorter than the bond *h* linking the two aryl nuclei, and in other respects there is a close similarity in the geometry of the two molecules, although the small and large angles in the pyridine rings A-F alternate in the opposite way to the corresponding bond angles in phenanthrene.



(12)



(13)

²⁶ G. Donnay, J. D. H. Donnay, and M. J. C. Harding, *Acta Crystallogr.* **19**, 688 (1965).

²⁷ M. Sen, *Acta Crystallogr., Sect. B* **30**, 556 (1974).

²⁸ J. V. Rund and P. C. Keller, *J. Chem. Soc. A*, 2827 (1970).

²⁹ D. K. Sen, *Acta Crystallogr., Sect. B* **25**, 988 (1969).

³⁰ B. A. Frenz and J. A. Ibers, *Inorg. Chem.* **11**, 1109 (1972).

³¹ I. Goldberg and U. Shmueli, *Cryst. Struct. Commun.* **2**, 175 (1973).

³² J. Trotter, *Acta Crystallogr.* **16**, 605 (1963).

TABLE II
MEAN BOND LENGTHS AND ANGLES IN PHENANTHRENE AND 1,10-PHENANTHROLINE

Bond	Bond length (Å)			Angle	Angle (°)		
	Phenanthrene ³²	1,10-Phenanthroline			Phenanthrene ³²	1,10-Phenanthroline	
		Ref. 30 ^a	Ref. 31 ^b			Ref. 30 ^a	Ref. 31 ^b
<i>a</i>	1.38	1.34	1.34	A	117	121	121
<i>b</i>	1.40	1.41	1.39	B	123	119	118
<i>c</i>	1.38	1.33	1.34	C	120	122	125
<i>d</i>	1.40	1.36	1.36	D	122	119	116
<i>e</i>	1.40	1.42	1.41	E	118	122	120
<i>f</i>	1.46	1.39	1.42	F	122	117	118
<i>g</i>	1.39	1.43	1.42	G	120	117	121
<i>h</i>	1.45	1.41	1.45	H	119	120	118
<i>i</i>	1.37	1.32	1.36	I	121	122	120

^a Values are for the tris(1,10-phenanthroline)nickel(II) pentacarbonylmanganate complex.

^b Values are for the 1 : 1 complex of 1,10-phenanthroline with 7,7,8,8-tetracyano-*p*-quinodimethane.

X-Ray diffraction studies of complexes of 2,9-dimethyl-1,10-phenanthroline (cf. e.g. Preston and Kennard³³ and Power³⁴) and 2,4,7,9-tetramethyl-1,10-phenanthroline (e.g., Canty and Gatehouse³⁵) and the overcrowded molecule, 1,10-dichloro-3,8-dimethyl-4,7-phenanthroline,³⁶ have also been determined.

B. THEORETICAL AND QUANTUM CHEMICAL CALCULATIONS

Several groups have applied theoretical and quantum chemical calculations to many aspects of the phenanthrolines over the past two decades. The π -electron distributions in all the phenanthrolines have been determined, and they are generally in accord with the known chemical reactions of the molecules.³⁷ Resonance energies of 1,7- and 1,10-phenanthrolines have been calculated and compared with those of 7-aminoquinoline and 8-aminoquinoline, respectively.³⁸ Calculations applied to 1,10-phenanthroline and methyl-substituted derivatives have been correlated with their reduction potentials³⁹ and ionization constants.⁴⁰ Bond lengths for most of the phenanthrolines have been computed.⁴¹

There has been interest in the theoretical treatment of the spectra of the phenanthrolines. Correlations between nuclear magnetic resonance (NMR)⁴²⁻⁴⁸ and electronic spectra^{22, 38, 40, 41, 49-51} with various quantum chemical data have been discussed. Often there is reasonable agreement between the calculated and measured spectra.

³³ H. S. Preston and C. H. L. Kennard, *J. Chem. Soc. A*, 2955 (1969).

³⁴ L. F. Power, *Inorg. Nucl. Chem. Lett.* **6**, 791 (1970).

³⁵ A. J. Canty and B. M. Gatehouse, *Acta Crystallogr., Sect. B* **28**, 1872 (1972).

³⁶ F. H. Herbstein, M. Kapon, and D. Rabinovich, *Isr. J. Chem.* **10**, 537 (1972).

³⁷ H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.*, 971 (1949).

³⁸ E. B. Nyquist and M. M. Joullié, *J. Heterocycl. Chem.* **4**, 539 (1967).

³⁹ R. Held, F. Dietz, and P. Thomas, *Z. Chem.* **12**, 346 (1972).

⁴⁰ N. Sanders and P. Day, *J. Chem. Soc. A*, 1190 (1970).

⁴¹ B. Tinland, *Tetrahedron* **25**, 583 (1969).

⁴² H. Rosenberger, M. Pettig, and K. Madeja, *Z. Chem.* **6**, 30 (1966).

⁴³ H. H. Perkampus, *Z. Naturforsch. A* **22**, 1430 (1967).

⁴⁴ J. Kuthan and V. Skala, *Z. Chem.* **6**, 422 (1966).

⁴⁵ H. Rosenberger, M. Pettig, K. Madeja, and G. Klose, *Ber. Bunsenges. Phys. Chem.* **72**, 847 (1968).

⁴⁶ H. Rosenberger, M. Pettig, K. Madeja, G. Engelhardt, and R. Radeglia, *Ber. Bunsenges. Phys. Chem.* **73**, 662 (1969).

⁴⁷ U. Haubenreisser, H. Rosenberger, and K. Madeja, *Z. Phys. Chem. (Leipzig)* **244**, 401 (1970).

⁴⁸ J. Mlochowski and W. Sliwa, *Rocz. Chem.* **48**, 1469 (1974).

⁴⁹ H. H. Perkampus, J. V. Knop, A. Knop, and G. Kassebeer, *Z. Naturforsch. A* **22**, 1419 (1967).

⁵⁰ L. I. Savranskii, *Zh. Prikl. Spektrosk.* **13**, 1084 (1970) [*CA* **74**, 81324 (1971)].

⁵¹ M. Berndt and W. Woznicki, *Acta Phys. Pol. A* **43**, 101 (1973) [*CA* **78**, 90502 (1973)].

The triplet state of the phenanthrolines has interested several groups, frequently in conjunction with electron paramagnetic resonance (EPR) transitions.^{22,52-60} Electron spin densities in radical cations and anions of 1,10-phenanthrolines have been calculated.^{61,62} The binding energies of N-1 in salts of 1,10-phenanthroline have been studied using X-ray photoelectron spectroscopy.⁶³

C. DIPOLE MOMENTS

The dipole moment of 1,10-phenanthroline was first measured by Fielding and Le Fèvre,¹⁸ who obtained a moment of 4.1 D, close to the value of 3.8 D expected for the hypothetical *cis*-2,2'-bipyridyl. Since then the dipole moments of the phenanthrolines have been studied by other groups.^{16,17,64} The experimental values are recorded in Table I. They were found to be in good agreement with values computed by the vector addition of the moments of the individual pyridine nuclei. The molecular polarizability of 1,10-phenanthroline has been further studied and its molar Kerr constant determined.⁶⁵

D. SPECTRA

Reference to all the spectra of the numerous phenanthrolines that have been examined is beyond the scope of the review. This section covers studies on the parent phenanthrolines and gives key references to substituted derivatives. Several references to spectral data that are of especial value in particular applications, such as structure elucidation, are mentioned in later sections of the article.

⁵² G. P. Rabold and L. H. Piette, *Photochem. Photobiol.* **5**, 733 (1966).

⁵³ H. H. Perkampus and A. Knop, *Z. Naturforsch. A* **23**, 849 (1968).

⁵⁴ G. P. Rabold and L. H. Piette, *Spectrosc. Lett.* **1**, 225 (1968).

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⁵⁶ Y. Gondo and Y. Kanda, *Bull. Chem. Soc. Jpn.* **43**, 3943 (1970).

⁵⁷ J. de Jong and C. Maclean, *Chem. Phys. Lett.* **5**, 424 (1970).

⁵⁸ J. de Jong, *J. Magn. Reson.* **9**, 185 (1973).

⁵⁹ A. Chodkowska and Z. R. Grabowski, *Chem. Phys. Lett.* **24**, 11 (1974).

⁶⁰ S. K. Morshnev, *Zh. Prikl. Spektrosk.* **23**, 428 (1975) [*CA* **83**, 192057 (1975)].

⁶¹ C. L. Honeybourne and S. Morris, *Chem. Phys. Lett.* **11**, 380 (1971).

⁶² C. L. Honeybourne, *Mol. Phys.* **21**, 1057 (1971).

⁶³ L. E. Cox, J. J. Jack, and D. M. Hercules, *J. Am. Chem. Soc.* **94**, 6575 (1972).

⁶⁴ A. Sucharda-Sobczyk, L. Sobczyk, J. Mlochowski, and A. Koll, *Rocz. Chem.* **48**, 1265 (1974).

⁶⁵ P. H. Cureton, C. G. Le Fèvre, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1736 (1963).

1. Infrared and Raman Spectra

The infrared (IR) spectra of 1,10-phenanthroline, its hydrate and perchlorate in the region $600\text{--}2000\text{ cm}^{-1}$ have been obtained, and the principal features of the spectra interpreted.⁶⁶ Further studies on the IR spectra of 1,10-phenanthroline,^{67–69} substituted 1,10-phenanthrolines,^{70,71} and 1,7-phenanthroline⁶⁷ have also been reported. The IR spectrum of 4,7-phenanthroline in the region $650\text{--}900\text{ cm}^{-1}$ has been analyzed, and the C–H out-of-plane deformation frequencies were compared with those of phenanthrene and benzo[*f*]quinoline.⁷² The IR spectra of salts of 1,10-phenanthroline have been taken, and the NH vibrations determined.^{28,73} Infrared spectroscopy has been used to detect water associated with 1,10-phenanthroline and some of its derivatives on extraction into nitromethane from aqueous solution.⁷⁴ The Raman spectrum of 1,10-phenanthroline has been compared with its IR spectrum.⁷⁵ Recently, the Raman and IR spectra of all ten isomeric phenanthrolines were measured in solution and solid states, and the spectra were fully discussed.⁷⁶

2. Fluorescence and Phosphorescence Spectra

The influence of the presence of nitrogen atoms on the fluorescence and phosphorescence spectral maxima of aromatic molecules has been discussed, including comparison of the spectra of phenanthrene and 1,10-phenanthroline, the spectral maxima of which are similar.⁷⁷

The fluorescence spectra of 1,7-phenanthroline,^{22,78} 1,10-phenanthroline,^{22,78–82} substituted 1,10-phenanthrolines,^{80,83} 4,7-

⁶⁶ A. A. Schilt and R. C. Taylor, *J. Inorg. Nucl. Chem.* **9**, 211 (1959).

⁶⁷ H. H. Perkampus and E. Baumgarten, *Z. Elektrochem.* **64**, 951 (1960).

⁶⁸ R. G. Inskeep, *J. Inorg. Nucl. Chem.* **24**, 763 (1962).

⁶⁹ S. S. Singh, *Z. Naturforsch. A* **24**, 2015 (1969).

⁷⁰ E. C. M. Grigg, J. R. Hall, and R. A. Plowman, *Aust. J. Chem.* **15**, 425 (1962).

⁷¹ E. C. M. Grigg and J. R. Hall, *Aust. J. Chem.* **15**, 864 (1962).

⁷² R. H. Wiley, C. H. Jarboe, and F. N. Hayes, *J. Org. Chem.* **23**, 268 (1958).

⁷³ Z. Dega-Szafran, *Rocz. Chem.* **43**, 823 (1969).

⁷⁴ S. Burchett and C. E. Meloan, *J. Inorg. Nucl. Chem.* **34**, 1207 (1972).

⁷⁵ K. Krishnan and R. A. Plane, *Spectrochim. Acta, Part A* **25**, 841 (1969).

⁷⁶ H. H. Perkampus and W. Rother, *Spectrochim. Acta, Part A* **30**, 597 (1974).

⁷⁷ S. G. Schulman, *Fluoresc. News* **7**, 33 (1973).

⁷⁸ H. Gropper and F. Doerr, *Ber. Bunsenges Phys. Chem.* **67**, 46 (1963).

⁷⁹ J. Messier, M. Vandevyver, and G. Marc, *C.R. Hebd. Seances Acad. Sci., Ser. B.* **269**, 1165 (1969).

⁸⁰ M. A. West, K. J. McCallum, R. J. Woods, and S. J. Formosinho, *Trans. Faraday Soc.* **66**, 2135 (1970).

⁸¹ S. G. Schulman, P. T. Tidwell, J. J. Cetorelli, and J. D. Winefordner, *J. Am. Chem. Soc.* **93**, 3179 (1971).

phenanthroline,^{22,78} and substituted 4,7-phenanthrolines⁷² have been obtained in various conditions. The spectra of all ten phenanthrolines have been measured in ethanol-ether and heptane solutions.⁸⁴ Polarization of the fluorescence spectra has also been investigated.^{78,84} The fluorescence spectra at various pH values have been used to show that the excited singlet state of 1,10-phenanthroline is more basic than the ground and excited triplet states for the ionization of 1,10-phenanthroline to the 1,10-phenanthrolinium monocation.^{22,81,85} From investigation of the fluorescence spectrum, an excited-state dimerization of 1,10-phenanthroline has been detected in basic solution.⁸⁶

The phosphorescence spectra of the phenanthrolines have also been studied. The spectra of 1,7-phenanthroline,^{22,78} 1,10-phenanthroline,^{22,78-80,82,87-89} substituted 1,10-phenanthrolines,⁸⁰ and 4,7-phenanthroline^{22,78} have been measured in a variety of conditions. The phosphorescence spectra of all the parent phenanthrolines have been obtained in heptane.⁸⁴ The degree of polarization of the phosphorescence has also been investigated.^{78,84,90} The lifetime of the phosphorescence of 1,10-phenanthroline, which is less than that of phenanthrene,⁸⁸ has been well investigated.^{54,55,80,89,91} The ionization constants of the excited triplet state of 1,10-phenanthroline have been calculated from the phosphorescence spectra.^{22,88}

3. Ultraviolet Absorption Spectra

The ultraviolet absorption spectra of 1,7-phenanthroline,^{19,20,22,64} 1,8-phenanthroline,⁶⁴ 1,10-phenanthroline,^{18-20,23,24,64,92-95} 2,7-phenanthroline,⁶⁴ and 4,7-phenanthroline^{19,22,64} have been measured by several groups in different solvents and at various pH values in aqueous solution. Examples of the spectra of substituted 1,7-phenanthro-

⁸² M. K. De Armond and J. E. Hillis, *J. Chem. Phys.* **54**, 2247 (1971).

⁸³ P. Levillain and R. Bourdon, *Bull. Soc. Chim. Fr.*, 371 (1972).

⁸⁴ H. H. Perkampus, A. Knop, and J. V. Knop, *Z. Naturforsch.* **A 23**, 840 (1968).

⁸⁵ S. C. Lahiri and S. Aditya, *Indian J. Chem.* **9**, 492 (1971).

⁸⁶ C. J. Hensler and C. V. Banks, *Spectrochim. Acta, Part A* **29**, 453 (1973).

⁸⁷ M. D. Khalupovskii, *Opt. Spektrosk.* **11**, 617 (1961) [*CA* **56**, 9589 (1962)].

⁸⁸ J. S. Brinen, D. D. Rosebrook, and R. C. Hirt, *J. Phys. Chem.* **67**, 2651 (1963).

⁸⁹ H. Basara, A. Olszowski, and Z. Ruziewicz, *Bull. Acad. Pol. Sci., Ser. Sci., Math., Astron. Phys.* **22**, 93 (1974) [*CA* **80**, 81540 (1974)].

⁹⁰ F. Doerr and H. Gropper, *Angew. Chem., Int. Ed. Engl.* **1**, 332 (1962).

⁹¹ W. Halper and M. K. De Armond, *Chem. Phys. Lett.* **24**, 114 (1974).

⁹² G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.*, 3199 (1951).

⁹³ W. H. McCurdy and G. F. Smith, *Analyst* **77**, 846 (1952).

⁹⁴ G. M. Badger and I. S. Walker, *J. Chem. Soc.*, 122 (1956).

⁹⁵ P. J. Secrest, J. A. Pawley, and C. A. Lucchesi, *Appl. Spectrosc.* **13**, 141 (1959).

lines,^{96,97} 1,10-phenanthrolines,^{83,93,98-100} and 4,7-phenanthrolines^{20,101} are also worthy of note.

The UV spectra of all ten of the parent phenanthrolines in hexane or heptane solution were taken by Perkampus and Kassebeer.¹² Their

TABLE III
ULTRAVIOLET SPECTRA OF THE PHENANTHROLINES^a

Phenanthroline	λ_{\max} , nm (log ϵ) ^b
1,7	227(4.67), 232(4.75), 266(4.46), 308(2.95), 313(2.75), 322(2.84), 327(2.54), 337(2.46), 344sh(1.15)
1,8	215 (4.33), 231(4.57), 261(4.25), 277sh(3.95), 290(3.86), 309sh(3.05), 316(3.23), 322sh(3.12), 332(3.50), 337(3.17), 345(3.60), 353(3.00)
1,9	212(4.20), 238(4.63), 256sh(4.18), 282sh(3.71), 299(3.30), 305(3.21), 312(3.50), 319(3.38), 326(3.84), 333(3.43), 341(3.96)
1,10	226(4.63), 232(4.73), 263(4.42), 273sh(4.19), 288sh(3.72), 309(3.04), 313sh(2.89), 324(2.78), 329(2.54), 338(1.95)
2,7	211(4.33), 238(4.65), 265(4.10), 299(3.27), 306(3.23), 312(3.54), 319(3.44), 326(3.88), 333(3.48), 343(4.00)
2,8	242(4.59), 260sh(4.09), 273sh(3.96), 283(3.95), 295(3.80), 310(3.13), 317(2.89), 324(3.31), 334(2.78), 339(3.40)
2,9	212(4.20), 222(4.22), 244(4.65), 277sh(3.90), 292(3.76), 306sh(2.90), 314(2.97), 323sh(2.81), 328(3.18), 337(2.75), 344(3.21)
3,7	215sh(4.31), 230(4.62), 263(4.27), 297(3.90), 307(3.00), 314(3.24), 321sh(3.10), 325sh(3.18), 328(3.51), 336(3.07), 340(3.13), 344(3.61)
3,8	215(4.38), 235(4.62), 240(4.67), 259sh(3.95), 268(3.93), 278(4.08), 290(4.03), 308(2.94), 322(3.30), 337(3.61), 348(3.47), 353(3.71)
4,7	204(4.57), 214(4.26), 227(4.65), 233(4.76), 270(4.42), 282sh(4.21), 308(3.01), 314(2.88), 322(2.89), 328(2.70), 338(2.64)

^a From Perkampus and Kassebeer,¹² reprinted with permission.

^b In hexane or heptane.

results are given in modified form in Table III. The spectra are very similar to that of phenanthrene. Strong absorptions occur at about λ 210–270 nm, and a group of small absorption bands at about 290–350 nm.

⁹⁶ A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.* **2**, 120 (1965).

⁹⁷ G. P. Bean, M. J. Cook, T. M. Dand, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. B*, 2339 (1971).

⁹⁸ D. E. Zacharias and F. H. Case, *J. Org. Chem.* **27**, 3878 (1962).

⁹⁹ S. C. Lahiri and S. Aditya, *J. Indian Chem. Soc.* **41**, 469 (1964).

¹⁰⁰ S. C. Lahiri, *Z. Phys. Chem. (Leipzig)* **255**, 23 (1974).

¹⁰¹ A. L. Searles and R. M. Warren, *J. Org. Chem.* **18**, 1317 (1953).

The spectrum of 1,10-phenanthroline in polarized light¹⁰² has also been compared with that of phenanthrene.¹⁰³

4. Nuclear Magnetic Resonance Spectra

The proton NMR spectrum of 1,10-phenanthroline has been obtained and analyzed by several authors in nonaqueous solvents¹⁰⁴⁻¹⁰⁹ and in water at various pH values.^{28,110} Examples of studies of the NMR spectra of substituted 1,10-phenanthrolines that have been investigated in some detail are also worthy of mention.^{47,104,106,110} The NMR spectra of all ten phenanthrolines have been determined in deuteriochloroform, and the spectra were interpreted¹² (Table IV). The spectra of the 1,7-, 1,10-, and 4,7-isomers have also been compared with that of phenanthrene.¹¹¹ Shifts in the NMR spectrum of 1,10-phenanthroline induced by a europium shift reagent have been discussed,¹¹² and ¹³C chemical shifts of free and protonated 1,10-phenanthroline were measured.¹¹³

5. Mass Spectra

The mass spectra of all the parent phenanthrolines have been reported.¹¹⁴ As expected, the spectra are dominated by the peak due to the molecular ion, and there is relatively little fragmentation. The mass spectra of some oxidation products of 1,10-phenanthroline have also been briefly described.^{115, 115a}

¹⁰² B. Norden, R. Hakansson, and M. Sundbom, *Acta Chem. Scand.* **26**, 429 (1972).

¹⁰³ T. Hoshi, H. Inoue, J. Yoshino, T. Masamoto, and Y. Tanizaki, *Z. Phys. Chem. (Frankfurt)* **81**, 23 (1972).

¹⁰⁴ K. Ito, T. Isobe and K. Sone, *J. Chem. Phys.* **31**, 861 (1959).

¹⁰⁵ E. Vander Donckt, R. H. Martin, and F. Geerts-Evrard, *Tetrahedron* **20**, 1495 (1964).

¹⁰⁶ R. M. Carman and J. R. Hall, *Aust. J. Chem.* **17**, 1354 (1964).

¹⁰⁷ J. D. Miller and R. H. Prince, *J. Chem. Soc.* 4706 (1965).

¹⁰⁸ D. J. Blears and S. S. Danyluk, *Tetrahedron* **23**, 2927 (1967).

¹⁰⁹ M. Ohtsuru, K. Tori, and H. Watanabe, *Chem. Pharm. Bull (Tokyo)* **15**, 1015 (1967).

¹¹⁰ J. D. Miller and R. H. Prince, *J. Chem. Soc.*, 3185 (1965).

¹¹¹ R. H. Martin, N. Defay, F. Geerts-Evrard, and D. Bogaert-Verhoogen, *Tetrahedron Suppl.* **8**, Part 1, 181 (1966).

¹¹² W. L. F. Armarego, T. J. Batterham, and J. R. Kershaw, *Org. Magn. Reson.* **3**, 575 (1971).

¹¹³ H. Rosenberger, M. Pettig, K. Madeja, T. Pehk, and E. Lippmaa, *Org. Magn. Reson.* **2**, 329 (1970).

¹¹⁴ H. Budziekiewicz, V. Kramer, and H. H. Perkampus, *Z. Naturforsch. B* **25**, 178 (1970).

¹¹⁵ R. D. Gillard and R. E. E. Hill, *J. Chem. Soc., Dalton Trans.*, 1217 (1974).

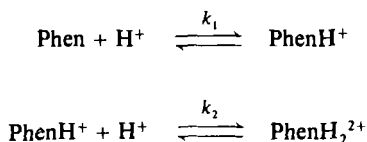
^{115a} N. G. Keats and L. A. Summers, *J. Heterocycl. Chem.* **12**, 1025 (1975).

6. Electron Paramagnetic Resonance Spectra

The electron spin resonance (ESR) spectrum of the radical anion of 1,10-phenanthroline obtained by reduction of 1,10-phenanthroline with sodium has been measured, and hyperfine splitting constants were assigned.¹¹⁶

E. IONIZATION PROPERTIES

The phenanthrolines are di-acidic bases. The two acid dissociation constants, k_1 and k_2 , for all the phenanthrolines have been determined. Typical values are recorded in Table I. Thermodynamic data for the equilibria have also been obtained.^{20, 21, 117-120}



There has been considerable interest in the first dissociation constant, k_1 , of substituted 1,10-phenanthrolines due to their use as metal complexing agents. In general the order of relative basic strengths of the derivatives of 1,10-phenanthroline is as expected. Electron-attracting substituents reduce the basicity whereas electron donating substituents increase the basicity of the molecule.^{24, 99, 121-127} The dissociation constants of several substituted phenanthrolines give good correlation with the extended Hammett equation.¹²⁸ Thermodynamic data on the

¹¹⁶ G. Gooijer, N. H. Velthorst, and C. MacLean, *Mol. Phys.* **24**, 1361 (1972).

¹¹⁷ R. Nasanen and E. Uusitalo, *Suom. Kemistil. B* **29**, 11 (1956) [*CA* **51**, 1698 (1957)].

¹¹⁸ R. Riccardi and P. Franzosini, *Boll. Sci. Fac. Chim. Ind. Bologna* **15**, 25 (1957) [*CA* **51**, 11014 (1957)].

¹¹⁹ F. Y. Kul'ba and Y. A. Makashev, *Zh. Obsch. Khim.* **32**, 1724 (1962) [*CA* **58**, 5102 (1963)].

¹²⁰ S. C. Lahiri and S. Aditya, *Z. Phys. Chem. (Frankfurt)* **41**, 173 (1964).

¹²¹ W. W. Brandt and D. K. Gullstrom, *J. Am. Chem. Soc.* **74**, 3532 (1952).

¹²² A. A. Schilt and G. F. Smith, *J. Phys. Chem.* **60**, 1546 (1956).

¹²³ H. Irving, M. J. Cabell, and D. H. Mellor, *J. Chem. Soc.*, 3417 (1953).

¹²⁴ M. Yasuda, K. Sone, and K. Yamasaki, *J. Phys. Chem.* **60**, 1667 (1956).

¹²⁵ H. Irving and D. H. Mellor, *J. Chem. Soc.*, 5237 (1962).

¹²⁶ W. A. E. McBryde, D. A. Brisbin, and H. Irving, *J. Chem. Soc.*, 5245 (1962).

¹²⁷ D. A. Brisbin and W. A. E. McBryde, *Can. J. Chem.* **41**, 1135 (1963).

¹²⁸ M. Charton, *J. Org. Chem.* **31**, 3739 (1966).

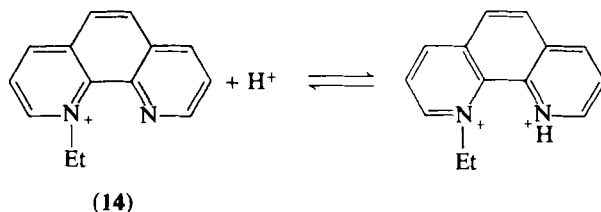
TABLE IV
PROTON NMR DATA OF THE PHENANTHROLINES^a

Phenanthroline	Chemical shift (δ) (ppm) in CDCl ₃									
	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	H ₉	H ₁₀
1,7	—	9.10	7.43	8.08	7.78	8.03	—	9.02	7.57	9.47
1,8	—	8.93	7.47	8.02	7.52	7.72	9.20	—	8.83	8.83
1,9	—	8.93	7.43	8.04	7.72	7.56	7.56	8.71	—	10.47
1,10	—	9.15	7.53	8.15	7.68	7.68	8.15	7.53	9.15	—
2,7	9.82	—	8.70	7.52	7.72	8.05	—	8.94	7.50	8.88
2,8	9.80	—	8.73	7.58	7.57	7.82	9.13	—	8.73	8.27
2,9	9.92	—	8.68	7.51	7.62	7.62	7.51	8.68	—	9.92
3,7	8.22	8.76	—	9.23	8.00	8.00	—	9.03	7.53	8.80
3,8	8.25	8.80	—	9.17	7.82	7.82	9.17	—	8.80	8.25
4,7	8.73	7.50	8.75	—	8.18	8.18	—	8.75	7.50	8.73

^a From Perkampus and Kassebeer,¹² reprinted by permission.

ionization constants of substituted 1,10-phenanthrolines¹²⁹⁻¹³² and 4,7-phenanthrolines²⁰ have also been recorded.

The most striking result in the list of dissociation constants in Table I is the very low pK_2 value for 1,10-phenanthroline compared with its isomers. 1,10-Phenanthroline was for long considered to be only a monoacidic base, unable to combine with a second proton in acid solution.¹³³ The reason for this was attributed to the closeness of the two nitrogen atoms (2.5 Å apart), which were thought to occupy positions such that electrostatic or steric forces prevented two protons from combining with the phenanthroline molecule. While this view is no longer tenable, the proximity of the nitrogen atoms is clearly largely responsible for the very low pK_2 value of 1,10-phenanthroline. The existence of the 1,10-PhenH₂²⁺ species in strong acid solution has been detected^{20, 23, 117, 134} spectroscopically. Studies of the second dissociation constant, K_2 of some methyl-substituted 1,10-phenanthrolines have also



been reported. As expected, the pK_2 values increase with methyl substitution, 2,9-dimethyl-1,10-phenanthroline, for example, having a pK_2 of about -0.3 .^{24, 25} The pK value for the protonation of the quaternary salt (14) is much lower, -2.80 , than for the protonation of the 1,10-phenanthroline ion owing to the steric effects of the *N*-alkyl group.¹³⁵

The actual structure of the 1,10-phenanthroline ion (1,10-PhenH⁺) is the subject of some doubt. 1,10-Phenanthroline commonly occurs in the solid state as the monohydrate, and in benzene solution there is an equilibrium established between the hydrate and the anhydrous base and water.¹³⁶ Hydrated forms of the phenanthroline ion have also been

¹²⁹ S. C. Lahiri and S. Aditya, *Z. Phys. Chem. (Frankfurt)* **43**, 282 (1964).

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¹³¹ S. C. Lahiri and S. Aditya, *J. Inorg. Nucl. Chem.* **30**, 2487 (1968).

¹³² S. C. Lahiri, *Z. Phys. Chem. (Leipzig)* **250**, 201 (1972).

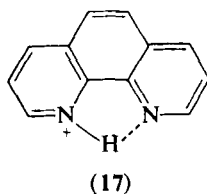
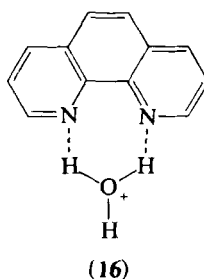
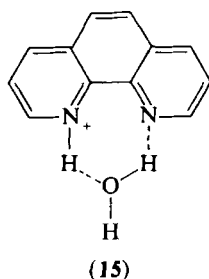
¹³³ T. S. Lee, I. M. Kolthoff, and D. L. Leussing, *J. Am. Chem. Soc.* **70**, 2348 (1948).

¹³⁴ D. W. Margerum, B. I. Bystroff, and C. V. Banks, *J. Am. Chem. Soc.* **78**, 4211 (1956).

¹³⁵ O. T. Benfey and J. W. Mills, *J. Am. Chem. Soc.* **93**, 922 (1971).

¹³⁶ I. R. Beattie and M. Webster, *J. Phys. Chem.* **66**, 115 (1962).

suggested,^{23, 128, 136} for example, the hydrogen-bonded forms **15** and **16**. Novel ionic species of the type $(1,10\text{-Phen})_2\text{H}^+$ and $(1,10\text{-Phen})_3\text{H}^+$ have also been proposed from potentiometric studies,¹³⁷ and an infrared and an X-ray study of solid compounds containing the $(1,10\text{-Phen})_2\text{H}^+$ ion have been reported.¹³⁸ Calorimetric and thermodynamic data applied to the reactions of 1,10-phenanthroline with hydrogen ion confirm the existence of the $(1,10\text{-Phen})_2\text{H}^+$ ion but cast doubts on the $(1,10\text{-Phen})_3\text{H}^+$ species.¹³⁹ The data also suggest that in the $1,10\text{-PhenH}^+$ ion the hydrogen is bound directly to the nitrogen atom through N—H covalent bonding, not through hydrogen bonding requiring water molecules. Infrared studies suggest a hydrogen-bonded form (**17**) for the 1,10-phenanthroline ion.¹⁴⁰



The protonation of 1,10-phenanthroline at different ionic strengths in the presence of various salts has been reported.^{141–143}

¹³⁷ M. J. Fahsel and C. V. Banks, *J. Am. Chem. Soc.* **88**, 878 (1966).

¹³⁸ M. P. Marzocchi and P. Paoletti, *Chem. Commun.*, 1063 (1968).

¹³⁹ P. Paoletti, A. Dei, and A. Vacca, *J. Chem. Soc. A*, 2656 (1971).

¹⁴⁰ L. Joris and P. von R. Schleyer, *Tetrahedron* **24**, 5991 (1968).

¹⁴¹ N. P. Komar and G. S. Zaslavskaya, *Zh. Anal. Khim.* **27**, 769 (1972) [*CA* **77**, 87602 (1972)].

¹⁴² N. P. Komar and G. S. Zaslavskaya, *Zh. Anal. Khim.* **28**, 360 (1973). [*CA* **78**, 147152 (1973)].

¹⁴³ N. P. Komar and G. S. Zaslavskaya, *Zh. Fiz. Khim.* **48**, 494 (1974) [*CA* **80**, 132592 (1974)].

F. CHROMATOGRAPHY

Experimental and theoretical studies of the separation of 1,7- and 1,10-phenanthrolines and some substituted derivatives in linear elution adsorption chromatography,^{144, 145} thin-layer chromatography,¹⁴⁶⁻¹⁴⁸ and liquid-liquid partition chromatography¹⁴⁹ have been described.

G. MISCELLANEOUS PROPERTIES

The polarographic behavior of 1,10-phenanthroline,¹⁵⁰⁻¹⁵² 1,7-phenanthroline,¹⁵³ and 4,7-phenanthroline¹⁵⁴ has been studied in aqueous solution, but the interpretation of the reduction waves is not always certain because of complications due to adsorption and catalytic hydrogen waves. Some substituted 1,10-phenanthrolines have also been investigated in this way.^{151, 155} Two clear reduction waves were obtained with 1,10-phenanthroline in dimethylformamide,¹⁵⁶ however, and an attempt was made to correlate the reduction potentials with the energy levels of the molecule. Other studies in nonaqueous solvents with 1,10-, 1,7-, and 4,7-phenanthrolines also gave distinct waves.^{151, 157}

1,10-Phenanthroline is a semiconductor. Its electrical conductivity is superior to that of phenanthrene and increases on melting.¹⁵⁸⁻¹⁶¹

The behavior of 1,10-phenanthroline on ion exchangers has been investigated.¹⁶²

¹⁴⁴ L. R. Snyder, *J. Chromatog.* **16**, 55 (1964).

¹⁴⁵ L. R. Snyder, *J. Chromatogr.* **17**, 73 (1965).

¹⁴⁶ L. H. Klemm, C. E. Klopfenstein, and H. P. Kelly, *J. Chromatogr.* **23**, 428 (1966).

¹⁴⁷ Y. Nishimoto and S. Toyoshima, *Yakugaku Zasshi* **85**, 317 (1965) [*CA* **63**, 12298 (1965)].

¹⁴⁸ H. Erlenmeyer and H. Bartels, *Helv. Chim. Acta* **48**, 301 (1965).

¹⁴⁹ E. Soczewinski and G. Matysik, *J. Chromatogr.* **32**, 458 (1968).

¹⁵⁰ M. T. Falqui, *Ann. Chim. (Rome)* **48**, 1135 (1958) [*CA* **53**, 12063 (1959)].

¹⁵¹ V. O. Gurtler, K. P. Dietz, and P. Thomas, *Z. Anorg. Allg. Chem.* **396**, 217 (1973).

¹⁵² M. K. Borenko, V. V. Shapovalov, and D. M. Palade, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **16**, 530 (1973) [*CA* **79**, 38004 (1973)].

¹⁵³ M. T. Falqui, *Ann. Chim. (Rome)* **48**, 1144 (1958) [*CA* **53**, 12063 (1959)].

¹⁵⁴ M. T. Falqui, *Ann. Chim. (Rome)* **49**, 1815 (1959) [*CA* **54**, 16229 (1960)].

¹⁵⁵ R. Zahradnik and K. Bocek, *Collect. Czech. Chem. Commun.* **26**, 1733 (1961).

¹⁵⁶ B. J. Tabner and J. R. Yandle, *J. Chem. Soc. A*, 381 (1968).

¹⁵⁷ S. Millefiori, *J. Heterocycl. Chem.* **7**, 145 (1970).

¹⁵⁸ P. K. Mitskevich and M. I. Bashmakova, *Zh. Fiz. Khim.* **38**, 1606 (1964) [*CA* **61**, 7817 (1964)].

¹⁵⁹ M. I. Bashmakova and P. K. Mitskevich, *Zh. Fiz. Khim.* **40**, 2260 (1966) [*CA* **66**, 6452 (1967)].

¹⁶⁰ M. I. Bashmakova and P. K. Mitskevich, *Elektrokhimiya* **2**, 700 (1966) [*CA* **65**, 8737 (1966)].

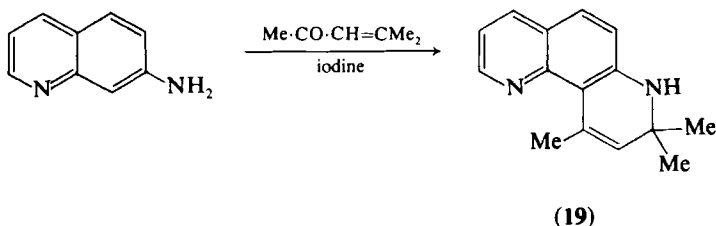
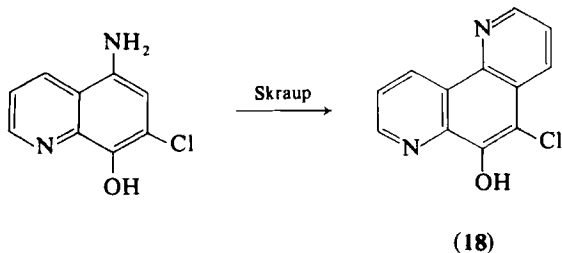
¹⁶¹ M. I. Bashmakova and A. I. Andrievskii, *Izv. Vyssh. Uchebn. Zaved., Fiz.* **11**, 140 (1968) [*CA* **69**, 81685 (1968)].

¹⁶² S. G. Iyer, P. K. Padmanabhan, and C. Venkateswarlu, *Anal. Chim. Acta* **70**, 475 (1974).

III. Syntheses

A. 1,7-PHENANTHROLINES

Improvements in the double Skraup synthesis of 1,7-phenanthroline from *m*-phenylenediamine now enable a yield of 70% to be achieved.¹⁶³ The Skraup reaction continues to be used for the synthesis of 1,7-phenanthrolines starting from the substituted 5-aminoquinolines. 5-Chloro-6-hydroxy-1,7-phenanthroline (**18**) has been prepared in this way,¹⁶⁴ and an improved synthesis of 6-hydroxy-1,7-phenanthroline was reported.¹⁶⁵ As expected, the Skraup reaction on 5-aminoquinoline affords 8-methyl-1,7-phenanthroline,¹⁶⁶ not 2-methyl-1,7-phenanthroline as it was previously named.⁸ The extension of the Skraup reaction using methyl vinyl ketone instead of glycerol has been applied to 5-aminoquinoline to afford 4-methyl-1,7-phenanthroline.¹⁶⁶ A related condensation using 2-hydroxymethylenecyclohexanone provides a route to benzo-substituted 1,7-phenanthrolines.¹⁶⁷ 7-Aminoquinoline with mesityl oxide in the presence of iodine gives 8,8,10-trimethyl-7,8-dihydro-1,7-phenanthroline (**19**).¹⁶⁸



¹⁶³ R. Lukes and J. Pliml, *Chem. Listy* **49**, 1836 (1955).

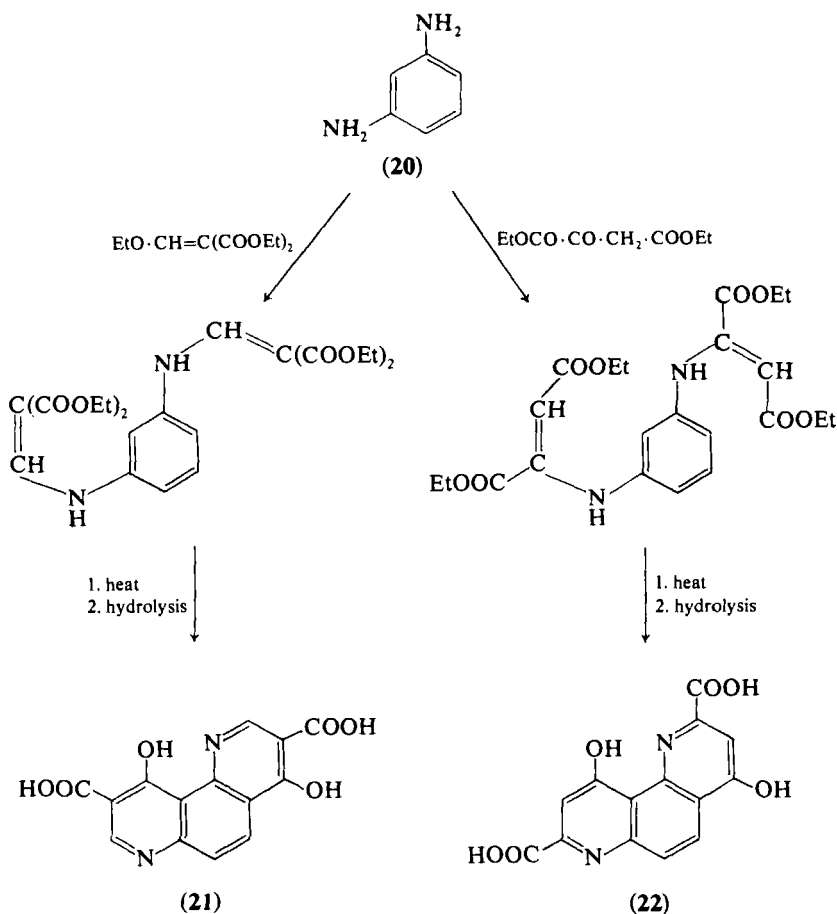
¹⁶⁴ F. X. Wiederkehr and E. Hofstetter, *Helv. Chim. Acta* **35**, 468 (1952).

¹⁶⁵ J. M. Duswalt and M. G. Mellon, *Anal. Chem.* **33**, 1782 (1961).

¹⁶⁶ R. L. Eifert and C. S. Hamilton, *J. Am. Chem. Soc.* **77**, 1818 (1955).

¹⁶⁷ H. M. Dali, V. N. Gogte, G. B. Mullick, and B. D. Tilak, *Indian J. Chem.* **12**, 1230 (1974).

¹⁶⁸ K. J. Liska, *J. Med. Chem.* **15**, 1177 (1972).



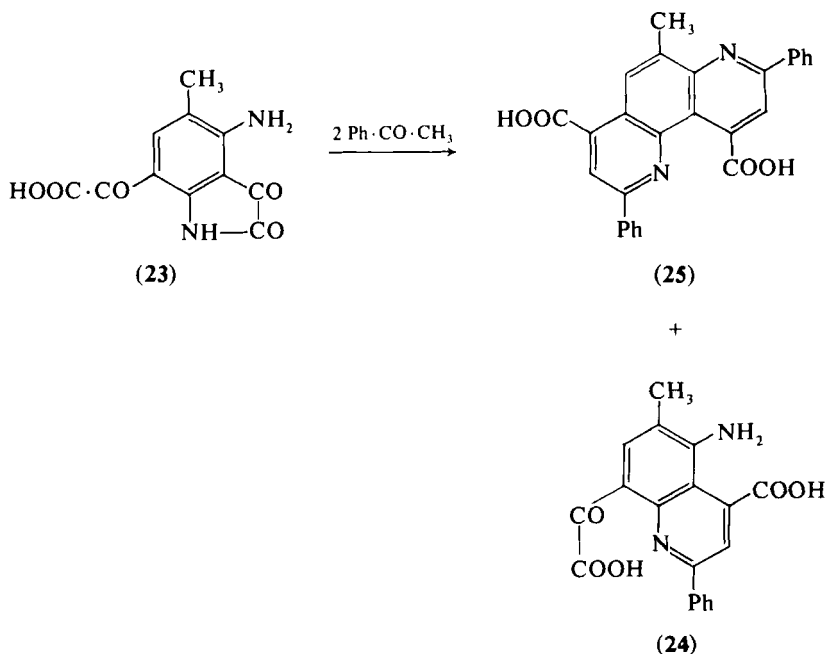
There have been some further examples of the use of the Conrad-Limpach reaction on substituted 5-aminoquinolines for the synthesis of 4-hydroxy-1,7-phenanthrolines, although the products (see Section IV,F,1) should properly be designated as phenanthrolineones.¹⁶⁹ Hot diphenyl ether is often employed as the medium for ring closure.¹⁷⁰ Ethyl trifluoro-acetoacetate has been used successfully in place of ethyl acetoacetate, and this variation has allowed entry to 2-trifluoromethyl-substituted 1,7-phenanthrolines.⁹⁶ Extensions of the Conrad-Limpach type of synthesis starting with *m*-phenylenediamine (**20**) and utilizing diethyl ethoxymethylene malonate or ethyl ethoxalylacetate, reagents frequently used in quinoline syntheses, have afforded, after hydrolysis,

¹⁶⁹ S. S. Chakravorti, B. Bhattacharya, and U. P. Basu, *Indian J. Chem.* **5**, 24 (1967).

¹⁷⁰ B. P. Bandiwala and C. M. Desai, *J. Indian Chem. Soc.* **31**, 927 (1954).

3,9-dicarboxy-4,10-dihydroxy-1,7-phenanthroline (21) and 2,8-dicarboxy-4,10-dihydroxy-1,7-phenanthroline (22), respectively.¹⁷¹ The structures were confirmed by conversion into 1,7-phenanthroline by decarboxylation, replacement of the hydroxyl groups by chlorine, and subsequent reductive dehalogenation. Similar condensations have been patented.^{172, 173} The former condensation has been extended to the synthesis of 3-carboethoxy-4-hydroxy-1,7-phenanthrolines from 5-aminoquinolines.^{174, 175} A similar condensation affording 4-hydroxy- and 10-hydroxy-1,7-phenanthrolines has been patented.¹⁷⁶

A related entry to the 1,7-phenanthroline ring system involves reaction of *m*-phenylenediamine with dimethyl acetylenedicarboxylate in methanol at ambient temperature.¹⁷⁷ This affords the intermediate bis-fumarate which cyclizes in diphenyl ether at 250° giving, in 95% yield, 2,8-dicarbomethoxy-4,10-dihydroxy-1,7-phenanthroline. The angular



¹⁷¹ A. R. Surrey and R. A. Cutler, *J. Am. Chem. Soc.* **76**, 1109 (1954).

¹⁷² A. R. Surrey, U.S. Patent 2,778,833 (1957) [*CA* **51**, 14831 (1957)].

¹⁷³ W. S. Waring, German Patent 2,220,294 (1972) [*CA* **78**, 29744 (1973)].

¹⁷⁴ R. L. Shivalkar and S. V. Sunthakar, *J. Sci. Ind. Res. (India)* **18B**, 447 (1959).

¹⁷⁵ S. Minami, M. Nakata, and M. Shimizu, Japanese Patent 55,698 (1974) [*CA* **82**, 156249 (1975)].

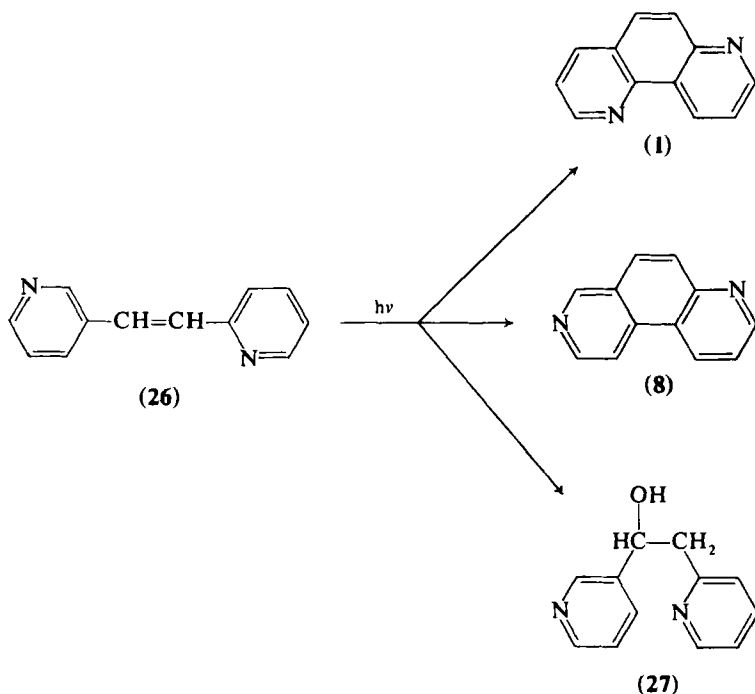
¹⁷⁶ Sterling Drug Co., British Patent 1,147,760 (1969) [*CA* **71**, 49967 (1969)].

¹⁷⁷ S. K. Khetan and M. V. George, *Can. J. Chem.* **47**, 3545 (1969).

fused structure was preferred over the alternative linearly fused one on NMR and IR evidence. *p*-Phenylenediamine, however, under similar conditions, gave a diazaanthracene rather than a 4,7-phenanthroline. This route was subsequently used to prepare several 1,7-phenanthrolines of interest as antiasthmatic agents.¹⁷⁸

2,8-Diphenyl-4,10-dicarboxy-6-methyl-1,7-phenanthroline (**25**) has been obtained¹⁷⁹ along with the quinoline derivative (**24**) by the alkaline condensation of acetophenone with the substituted isatin (**23**).

The photocyclization of appropriate 1,2-di(pyridyl)ethylenes provides a route to all the isomeric phenanthrolines, albeit sometimes in very low yield.¹² With *trans*-1-(2-pyridyl)-2-(3-pyridyl)ethylene (**26**) after irradiation in benzene solution in a stream of air, the hydrated product, 1-(2-pyridyl)-2-(3-pyridyl)ethan-2-ol (**27**) (20%) predominated, along with 3,7-phenanthroline (**8**) (6%) and 1,7-phenanthroline (**1**) (1%). The photocyclization process proceeds from the *trans* isomer by way of the *cis* isomer.^{179a}



¹⁷⁸ W. S. Waring, German Patent 2,149,692 (1972) [CA 77, 75201 (1972)].

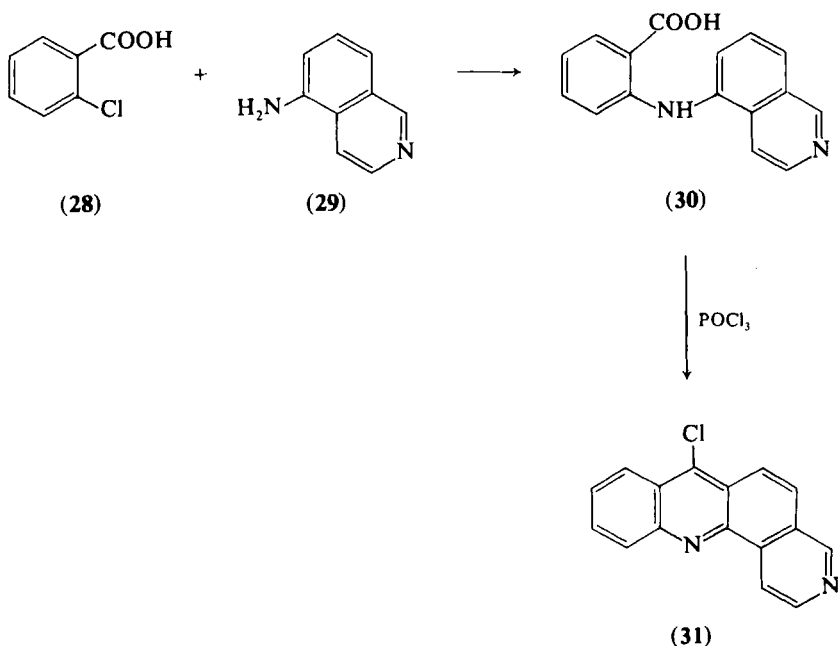
¹⁷⁹ Z. T. Allan, *Chem. Listy* 46, 224 (1952).

^{179a} H. H. Perkampus, G. Kassebeer, and P. Mueller, *Ber. Bunsenges. Phys. Chem.* 71, 40 (1967).

B. 1,8-PHENANTHROLINES

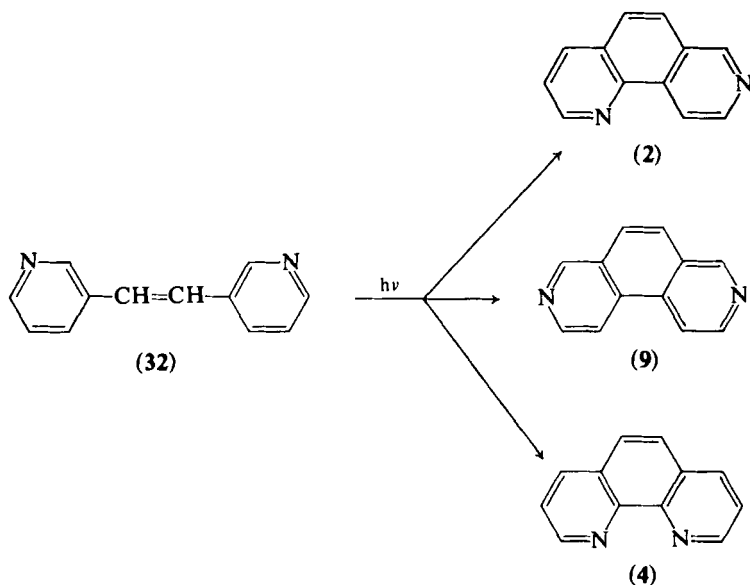
Modification of the Skraup synthesis of 1,8-phenanthroline from 5-aminoisoquinoline¹⁰ has improved the yield from 5% to 35%, thus making the route a feasible preparative one.¹⁴ The Conrad-Limpach synthesis of hydroxyphenanthrolines has been applied to 5-aminoisoquinoline using ethyl trifluoroacetoacetate as condensing agent and polyphosphoric acid as dehydrating agent. In this way, 4-hydroxy-2-trifluoromethyl-1,8-phenanthroline was prepared. It was shown to exist as the 1,8-phenanthrolin-4-one tautomer on IR and UV evidence.³⁸

7-Chlorobenzo[*b*][1,8]phenanthroline (31) has been prepared in a two-step synthesis from 5-aminoisoquinoline (29).¹⁸⁰ Condensation with *o*-chlorobenzoic acid (28) afforded *N*-(5-isoquinolyl)anthranilic acid (30) which was subsequently ring closed with phosphorus oxychloride. 7,10-Dichlorobenzo[*b*][1,8]phenanthroline was obtained likewise from 2,4-dichlorobenzoic acid.



Photocyclization of *trans*-1,2-di-(3-pyridyl)ethylene (32) in benzene afforded¹² a mixture of 1,8-phenanthroline (2) (12–20%), 3,8-phenanthroline (9) (~12%), and 1,10-phenanthroline (4) (1–2%).

¹⁸⁰ E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.* 5, 546 (1962).



C. 1,9-PHENANTHROLINES

The first synthesis of 1,9-phenanthroline was accomplished in 1966 by Perkampus and Kassebeer by the photocyclization of *trans*-1-(3-pyridyl)-2-(4-pyridyl)ethylene in benzene.¹² It was obtained pure in low yield (~4%) along with 2,8-phenanthroline (~35%). 1,9-Phenanthroline was subsequently obtained in 34% yield by a Skraup synthesis from 8-aminoisoquinoline.¹⁵ This reaction has been used by others.¹⁸¹

D. 1,10-PHENANTHROLINES

The importance of 1,10-phenanthroline and substituted 1,10-phenanthrolines as metal complexing agents and their use in analytical applications has provided the impetus for an extensive study of procedures for their synthesis.¹⁸² The original synthesis of 1,10-phenanthroline⁹ by a double Skraup reaction on *o*-phenylenediamine using glycerol and sulfuric acid in the presence of an oxidizing agent continues to attract attention, and various improvements in reaction

¹⁸¹ J. Mlochowski, W. Sliwa, and L. Achremowicz, *Rocz. Chem.* **48**, 787 (1974).

¹⁸² F. H. Case, "A Review of Synthesis of Organic Compounds Containing the Ferroin Group." Smith Chem. Co., Columbus, Ohio, 1960.

conditions giving better yields have been claimed.¹⁸³⁻¹⁸⁷ Yields up to 80% may be achieved if the product is continuously extracted from the crude reaction mixture.¹⁸⁸ Labeled [¹⁴C]-1,10-phenanthroline has also been obtained from [1-¹⁴C]glycerol in good yield.¹⁸⁹

Developments from the double Skraup synthesis using components other than glycerol to achieve ring extension have been reported¹⁹⁰⁻¹⁹⁶ although generally the yields do not compare favorably with the single Skraup ring closures starting from 8-aminoquinolines.

8-Aminoquinolines, therefore, remain the starting materials of choice for the synthesis of 1,10-phenanthrolines. Numerous modifications, extensions, and variations of the Skraup and Conrad-Limpach reactions have been developed, particularly by Case and his colleagues starting from 8-aminoquinolines.^{38,96,98,166,176,196-221} Attempts to apply

¹⁸³ G. K. Wheeler, U.S. Patent 2,651,636 (1953) [CA 49, 1824 (1955)].

¹⁸⁴ G. I. Mikhailov, *Khim. Tekhnol. Primen. Proizvodnykh Piridina Khinolina, Mater. Sovesch. Inst. Khim., Akad. Nauk. Latv. S.S.R. Riga* 283 (1957) [CA 55, 22316 (1961)].

¹⁸⁵ K. Madeja, *J. Prakt. Chem.* 17, 104 (1962).

¹⁸⁶ G. I. Mikhailov, *Tr. Vses. Nauchn.—Issled. Inst. Khim. Reaktivov* 25, 66 (1953) [CA 60, 14487 (1964)].

¹⁸⁷ B. Zak, Czech Patent 154,186 (1974) [CA 82, 16814 (1975)].

¹⁸⁸ T. Mazonski, A. Lachowicz, and M. Gruszczynski, *Zesz. Nauk. Politech. Slask., Chem.* 24, 207 (1964) [CA 63, 11526 (1965)].

¹⁸⁹ P. Ellis, R. G. Wilkins, and M. J. G. Williams, *J. Chem. Soc.*, 3975 (1956).

¹⁹⁰ L. S. Povarov and B. M. Mikhailov, *Izv. Akad. Nauk. SSR., Ser. Khim.* 1352 (1963) [CA 59, 12757 (1963)].

¹⁹¹ E. J. O'Reilly and R. A. Plowman, *Aust. J. Chem.* 13, 145 (1960).

¹⁹² G. Inoue, *Nippon Kagaku Zasshi* 79, 408 (1958) [CA 55, 6482 (1961)].

¹⁹³ B. Zak, Czech Patent 150,748 (1973) [CA 80, 95912 (1974)].

¹⁹⁴ B. Zak, Czech Patent 150,747 (1973) [CA 80, 95913 (1974)].

¹⁹⁵ B. Zak, Czech Patent 146,036 (1972) [CA 78, 124565 (1973)].

¹⁹⁶ F. H. Case and R. Sasin, *J. Org. Chem.* 20, 1330 (1955).

¹⁹⁷ K. Madeja, *J. Prakt. Chem.* 17, 97 (1962).

¹⁹⁸ N. D. Heindel and C. J. Ohnmacht, *J. Heterocycl. Chem.* 5, 869 (1968).

¹⁹⁹ F. H. Case, Z. B. Jacobs, R. S. Cook, and J. Dickstein, *J. Org. Chem.* 22, 390 (1957).

²⁰⁰ F. H. Case and P. F. Strohm, *J. Org. Chem.* 27, 1641 (1962).

²⁰¹ F. H. Case and J. A. Brennan, *J. Org. Chem.* 19, 919 (1954).

²⁰² J. R. Geigy AG, Swiss Patent 282,274 (1952) [CA 48, 7644 (1954)].

²⁰³ G. E. Calf and E. L. Samuel, *Aust. J. Chem.* 16, 833 (1963).

²⁰⁴ Monsanto Chemicals (Australia) Ltd., Netherlands Patent 6,409,934 (1965) [CA 63, 11519 (1965)].

²⁰⁵ F. H. Case and H. H. Wisneski, *J. Heterocycl. Chem.* 5, 789 (1968).

²⁰⁶ G. M. Badger, H. P. Crocker, and B. C. Ennis, *Aust. J. Chem.* 16, 840 (1963).

²⁰⁷ Monsanto Chemicals (Australia) Ltd., Netherlands Patent 6,410,619 (1965) [CA 63, 9946 (1965)].

²⁰⁸ E. Samuel and W. G. C. Raper, Australian Patent 261,910 (1965) [CA 69, 10426 (1968)].

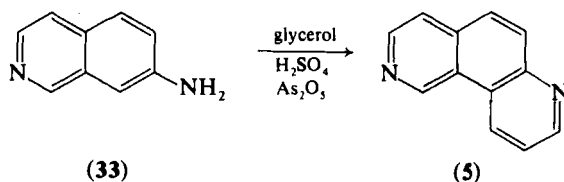
the Skraup reaction to 8-amino-5-trifluoromethylquinoline gave only 1,10-phenanthroline, the trifluoromethyl group being lost during the reaction, presumably by way of hydrolysis to the carboxylic acid followed by decarboxylation.²²²

The presence of 1,2,3,4-tetrahydro-3,4,7,8-tetramethyl-1,10-phenanthroline as a coproduct with 3,4,7,8-tetramethyl-1,10-phenanthroline from the reaction of 3,4-dimethyl-8-aminoquinoline with 3-methylbut-3-en-2-one is explained by disproportionation of the intermediate 1,2-dihydrophenanthroline.²⁰⁶

1,10-Phenanthroline is obtained in very low yield (1–2%) by the photocyclization of *trans*-1,2-di-(3-pyridyl)ethylene, along with 3,8- and 1,8-phenanthrolines.¹²

E. 2,7-PHENANTHROLINES

The first synthesis of 2,7-phenanthroline (**5**) was accomplished in 1966 by Perkampus and Kassebeer,¹² who obtained it in 23% yield by irradiating *trans*-1-(2-pyridyl)-2-(4-pyridyl)ethylene for several hours in benzene solution. It was obtained subsequently¹⁵ in 45% yield by a Skraup reaction on 7-aminoisoquinoline (**33**) (which was erroneously termed 7-aminoquinoline in the original paper). This reaction has been used by others.¹⁸¹



²⁰⁹ Monsanto Chemicals (Australia) Ltd., Netherlands Patent 6,410,620 (1965) [CA **63**, 11518 (1965)].

²¹⁰ K. C. John and F. H. Case, *J. Chem. Eng. Data* **13**, 568 (1968).

²¹¹ F. H. Case, *J. Org. Chem.* **21**, 1069 (1956).

²¹² M. J. Menendez, *An. Fac. Farm. Bioquim., Univ. Nac. Mayor San Marcos* **2**, 729 (1951) [CA **49**, 333 (1955)].

²¹³ J. Mlochowski and W. Sliwa, *Rocz. Chem.* **45**, 803 (1971).

²¹⁴ F. H. Case, *J. Heterocycl. Chem.* **7**, 647 (1970).

²¹⁵ M. Loy and M. M. Joullie, *J. Med. Chem.* **16**, 549 (1973).

²¹⁶ A. Richardson and F. J. McCarty, *J. Med. Chem.* **15**, 1203 (1972).

²¹⁷ S. Minami, Y. Takase, and S. Yamabe, Japanese Patent 49,797 (1973) [CA **79**, 105229 (1973)].

²¹⁸ F. H. Case, S. Catino, and F. Scholnick, *J. Org. Chem.* **19**, 31 (1954).

²¹⁹ E. Koft and F. H. Case, *J. Org. Chem.* **27**, 865 (1962).

²²⁰ E. Ziegler, E. Nolken, and H. Junek, *Monatsh. Chem.* **93**, 708 (1962).

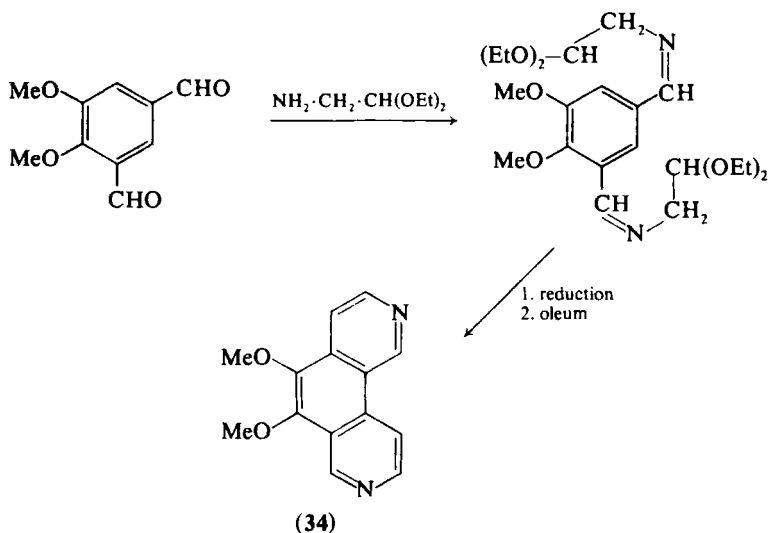
²²¹ K. H. Vogt and F. Hein, *J. Prakt. Chem.* **32**, 173 (1966).

²²² R. Belcher, M. Stacey, A. Sykes, and J. C. Tatlow, *J. Chem. Soc.*, 3846 (1954).

The Conrad-Limpach reaction has been applied successfully to 7-aminoisoquinoline using acetoacetic ester as condensing agent. In this way 8-methyl-10-hydroxy-2,7-phenanthroline was obtained.¹⁸¹

F. 2,8-PHENANTHROLINES

The first synthesis of a derivative of 2,8-phenanthroline was reported by Merz, Weidlich, and Fink¹³ in 1964. They prepared 5,6-dimethoxy-2,8-phenanthroline (**34**) (isolated as the dipicrate) in very low yield by conducting a double Pomeranz-Fritsch isoquinoline synthesis on 4,5-dimethoxyisophthalaldehyde. The parent compound was prepared 2 years later¹² in 25–35% yield, along with 1,9-phenanthroline (4%), by the photocyclization of *trans*-1-(3-pyridyl)-2-(4-pyridyl)ethylene in benzene. This reaction was used by Hünig and his colleagues¹⁵ to prepare an *N,N'*-dimethyl diquaternary salt of 2,8-phenanthroline by methylating the crude product from the irradiation reaction.



G. 2,9-PHENANTHROLINES

The only synthesis of 2,9-phenanthroline is that due to Perkampus and Kassebeer.¹² Irradiation of *trans*-1,2-di-(4-pyridyl)ethylene in benzene gave a 45% yield of 2,9-phenanthroline. In some reaction conditions small amounts of 5,6-dihydro-2,9-phenanthroline were also formed. This synthesis has subsequently been utilized and modified by Hünig and his colleagues.¹⁵

H. 3,7-PHENANTHROLINES

Likewise, the only synthesis of 3,7-phenanthroline is that due to Perkampus and Kassebeer.¹² Irradiation of a benzene solution of *trans*-1-(2-pyridyl)-2-(3-pyridyl)ethylene for 10 hours gave a 15% yield of 3,7-phenanthroline. If air was drawn through the system the hydrated product, 1-(2-pyridyl)-2-(3-pyridyl)ethan-2-ol (20%) predominated, along with 3,7-phenanthroline (6%) and 1,7-phenanthroline (~1%). The irradiation procedure was used subsequently.¹⁵

I. 3,8-PHENANTHROLINES

3,8-Phenanthroline was first claimed to have been synthesized by a double Pomeranz-Fritsch isoquinoline synthesis.¹¹ It has recently been prepared¹² in about 12% yield by the irradiation of *trans*-1,2-di(3-pyridyl)ethylene in benzene, along with 1,8-phenanthroline (12–20%) and 1,10-phenanthroline (1–2%). The melting point is quite different from that recorded earlier by Ruggli and Schetty.¹¹ This latter method has subsequently been used¹⁵ to prepare an *N,N'*-dimethyl diquaternary salt of 3,8-phenanthroline by methylating the crude product from the irradiation reaction.

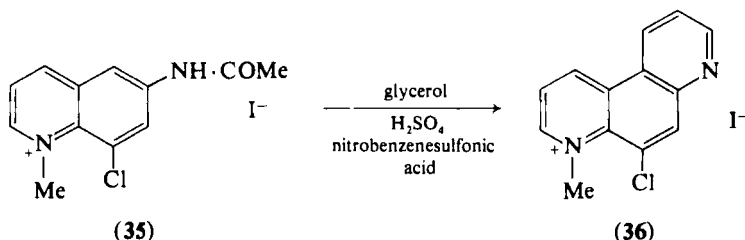
J. 4,7-PHENANTHROLINES

The original synthesis of 4,7-phenanthroline from *p*-phenylenediamine by a double Skraup reaction using glycerol, sulfuric acid, and an oxidizing agent has been modified so that yields of 60–75% may now be achieved. The improvement uses the *N,N'*-diacetyl derivative of *p*-phenylenediamine as starting material. The synthesis was conducted in the presence of ferrous sulfate, which serves to moderate the oxidizing conditions of the reaction.⁷² The product was purified by continuous extraction. The ethoxyacetal, 1,1,3-triethoxypropane, has been used in place of glycerol, and by heating it at 190° with *p*-phenylenediamine a 50% yield of 4,7-phenanthroline can be obtained.¹⁹⁰ With crotonaldehyde as condensing agent, 3,8-dimethyl-4,7-phenanthroline has been obtained from *p*-phenylenediamine.²²³ The double Skraup synthesis has also been applied to 2-methoxy-*p*-phenylenediamine to afford 5-methoxy-4,7-phenanthroline.^{224,225}

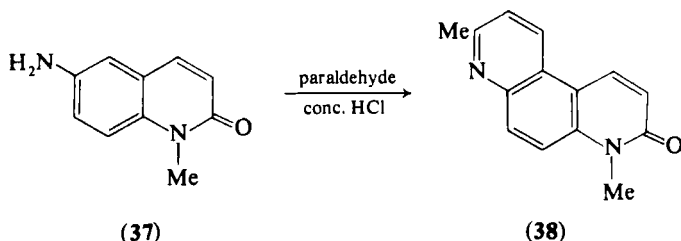
²²³ A. V. El'tsov, S. V. Nekrasov, and E. V. Smirnov, *Zh. Org. Khim.* **8**, 1309 (1972) [*CA* **77**, 153892 (1972)].

²²⁴ Ciba Ltd., British Patent 675,775 (1952) [*CA* **47**, 5456 (1953)].

²²⁵ I. Z. Protopopov, M. Kraft, A. Z. Vlasov, and T. Z. Kukushkina, German Patent 1,232,156 (1967) [*CA* **66**, 115700 (1967)].



Several examples have been reported of the preparation of 4,7-phenanthrolines from substituted 6-aminoquinolines by the Skraup and related reactions. In this way, 5-methoxy-,^{224, 226} 5-chloro-,²²⁷ 3-methyl-6-methoxy-,²²⁸ 1-methyl-,¹⁶⁶ and 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthrolines²²⁹ have been synthesized while improvements have been made to the synthesis of the 3-methyl derivative.²³⁰ The Skraup reaction has also been applied to quaternary salts of 6-aminoquinolines. For example, 5-chloro-4-methyl-4,7-phenanthroline iodide (36) was obtained from the methiodide of 6-acetamido-8-chloroquinoline (35).^{227, 229, 231} Cyclizations starting from aminocarbostyrils have also been reported. Thus, 6-amino-1-methylcarbostyril (37) was condensed with paraldehyde in the presence of concentrated hydrochloric acid to afford 3,4-dihydro-4,8-dimethyl-3-oxo-4,7-phenanthroline (38),²³⁰ while under Skraup conditions, with glycerol as condensing agent, 6-amino-4-methylcarbostyril afforded 3,4-dihydro-1-methyl-3-oxo-4,7-phenanthroline.²³² With 5-methyl-6-aminocarbostyril (39) the expected linear condensation product (40) was accompanied, predominantly, by the formation of 3,4-dihydro-3-oxo-4,7-phenanthroline (41), the methyl group apparently being oxidized, followed by decarboxylation, in the Skraup reaction conditions.²³³



²²⁶ B. Eistert and G. Fink, *Chem. Ber.* **95**, 2395 (1962).

²²⁷ W. O. Sykes, *J. Chem. Soc.*, 3543 (1953).

²²⁸ Ciba Ltd., Swiss Patent 290,516 (1953) [*CA* **49**, 7606 (1955)].

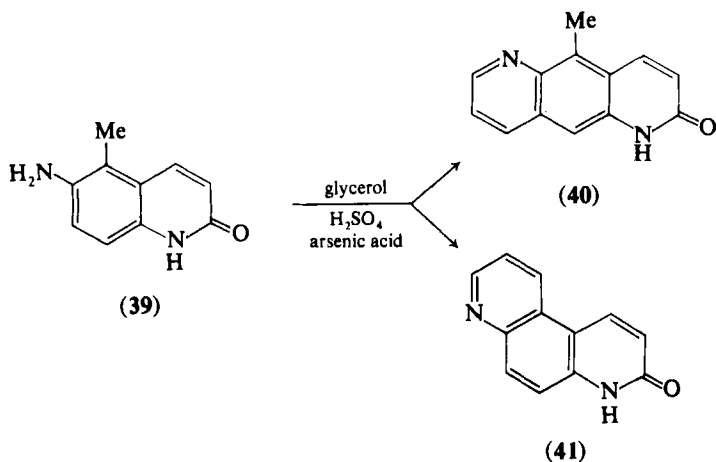
²²⁹ W. O. Sykes, *J. Chem. Soc.*, 4430 (1965).

²³⁰ W. O. Sykes, *J. Chem. Soc.*, 3087 (1956).

²³¹ W. O. Sykes, *J. Chem. Soc.*, 825 (1958).

²³² T. Yoshikawa, *Yakugaku Zasshi* **81**, 1323 (1961) [*CA* **56**, 7266 (1962)].

²³³ T. Yoshikawa, *Yakugaku Zasshi* **81**, 1601 (1961) [*CA* **56**, 11567 (1962)].



Applications of the Conrad–Limpach reaction to the synthesis of 1-hydroxy-4,7-phenanthrolines or, more correctly, 1-oxo-1,4-dihydro-4,7-phenanthrolines, from *p*-phenylenediamine or 6-aminoquinolines continue to be reported. 1,10-Dihydroxy-3,8-dimethyl-4,7-phenanthroline has again been prepared from *p*-phenylenediamine,²³⁴ hot diphenyl ether being used to effect the cyclization. Other examples include the new or improved preparations of 1-hydroxy-3-methyl-, 10-amino-1-hydroxy-3-methyl-,²³² 2-(γ -chlorocrotonyl)- 1,10-dihydroxy-3,8-dimethyl-, and 2,9-bis(γ -chlorocrotonyl)- 1,10-dihydroxy-3,8-dimethyl-4,7-phenanthrolines.²³⁵ Compounds prepared in this way have been patented as antiasthmatic agents.¹⁷⁸ A closely related synthesis employing polyphosphoric acid as cyclizing agent has yielded 1-hydroxy-3-phenyl-4,7-phenanthroline.²³⁶

A few extensions of the Conrad–Limpach synthesis have been applied to the synthesis of 4,7-phenanthrolines. Unlike *o*-phenylenediamine, which gives a quinoxaline derivative, *p*-phenylenediamine reacts with excess of ethyl ethoxalylpropionate to give an intermediate bisanil, which cyclizes in hot diphenyl ether to afford 3,8-dicarboethoxy-1,10-dihydroxy-2,9-dimethyl-4,7-phenanthroline in high yield.²³⁷ With diethyl ethoxymethylenemalonate as condensing agent, 6-amino-8-methoxyquinoline has been converted into 2-carboethoxy-1-hydroxy-6-methoxy-4,7-phenanthroline.²³⁸ A related condensation affording 1-

²³⁴ B. P. Bangdiwala and C. M. Desai, *J. Indian Chem. Soc.* **31**, 688 (1954).

²³⁵ L. V. Gyul'budagyan, E. E. Kaplanyan, and V. A. Grigoryan, *Arm. Khim. Zh.* **20**, 526 (1967) [*CA* **68**, 105047 (1968)].

²³⁶ J. Moszew and K. Bogdanowicz-Szwed, *Zesz. Nauk. Uniw. Jagiellon, Pr. Chem.*, **133** (1970) [*CA* **74**, 53590 (1971)].

²³⁷ Y. J. L'Italien and C. K. Banks, *J. Am. Chem. Soc.* **73**, 3246 (1951).

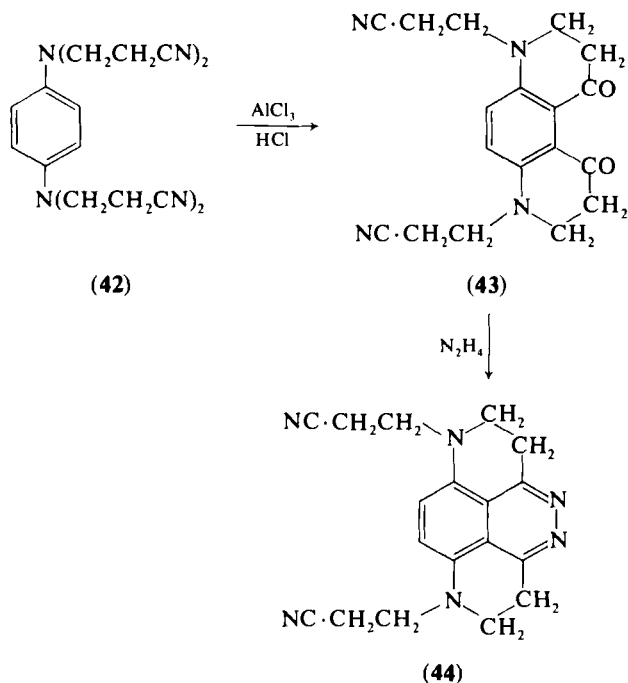
²³⁸ G. Y. Leshner, U.S. Patent 3,313,817 (1967) [*CA* **67**, 100129 (1967)].

hydroxy-4,7-phenanthroline from 6-aminoquinoline has been patented.¹⁷⁶

Further examples of the Knorr reaction for the synthesis of 3-hydroxy-4,7-phenanthrolines are reported. A modification of the original synthesis²³⁹ of 3-hydroxy-1-methyl-4,7-phenanthroline involves isolation of the intermediate acetoacetanilide followed by ring closure with sulfuric acid.²³² 10-Amino-3-hydroxy-1-methyl-4,7-phenanthroline was obtained similarly from 4-amino-6-acetoacetamidoquinoline. Several 2-substituted 1,3-dihydroxy-4,7-phenanthrolines were obtained likewise from diethyl alkylmalonates.¹⁰¹

There has been some interest in Doebner's pyruvic acid synthesis of 1-carboxy-4,7-phenanthrolines. The claim that 1,10-dicarboxy-3,8-diphenyl-4,7-phenanthroline is got by one-step synthesis from *p*-phenylenediamine²⁴⁰ is disputed,²⁴¹ although the synthesis of 1-carboxy-3,8-diphenyl-4,7-phenanthroline is accomplished from 6-amino-2-phenylquinoline.

A novel route to the 4,7-phenanthroline ring system involves cyclization of *N,N,N',N'*-tetrakis-2'-cyanoethyl-*p*-phenylenediamine



²³⁹ W. O. Kermack and A. P. Weatherhead, *J. Chem. Soc.*, 1164 (1940).

²⁴⁰ E. H. Woodruff and R. Adams, *J. Am. Chem. Soc.* **54**, 1977 (1932).

²⁴¹ J. E. A. Otterstedt and R. Pater, *J. Heterocycl. Chem.* **9**, 225 (1972).

(42) to 4,7-bis-2'-cyanoethyl-1,2,3,4,7,8,9,10-octahydro-1,10-dioxo-4,7-phenanthroline (43) with aluminum chloride and hydrochloric acid in chlorobenzene.²⁴² The structure was confirmed spectroscopically and by reaction with hydrazine, which gave the tetraazapyrene derivative (44).

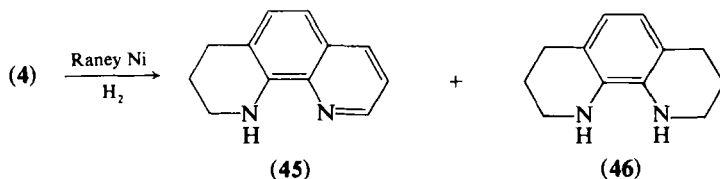
Irradiation of *trans*-1,2-di-(2-pyridyl)ethylene in benzene gives a low yield (5–8%) of 4,7-phenanthroline.¹²

IV. General Reactions

A. REDUCTION

1. 1,10-Phenanthroline

The reduction of 1,10-phenanthroline (4) occurs preferentially in the pyridine rings. Chemical reduction affords a low yield of 1,2,3,4-tetrahydro-1,10-phenanthroline,²⁴³ but hydrogenation with Raney nickel as catalyst gives good yields of the 1,2,3,4-tetrahydro (45) and/or the 1,2,3,4,7,8,9,10-octahydro (46) derivative depending on reaction conditions.²⁴⁴ Hydrogenation of certain substituted 1,10-phenanthrolines with Raney nickel likewise affords tetrahydro derivatives.^{38,96} The rings of 1,7-phenanthrolines, however, were not reduced under the same conditions.



2. 4,7-Phenanthroline

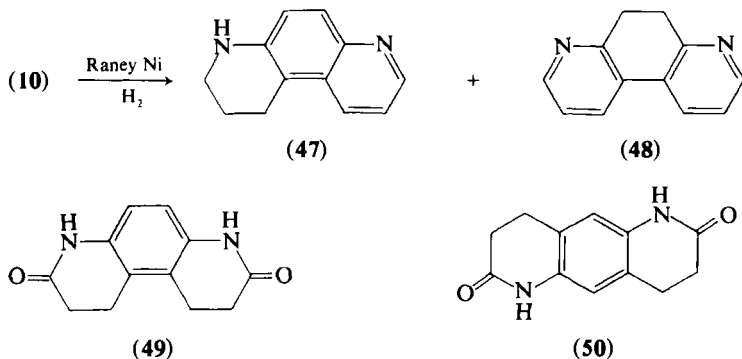
There has been considerable interest in the reduction of 4,7-phenanthrolines. Hydrogenation of 4,7-phenanthroline (10) under pressure with Raney nickel results in reduction of either the benzene ring or one of the pyridine rings. Both products, 5,6-dihydro- (48) and 1,2,3,4-tetrahydro-4,7-phenanthrolines (47), are formed in approximately equal amounts (40% yield).¹⁰¹ This result contrasts with an

²⁴² J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1817 (1953).

²⁴³ K. Hensen and U. Trobs, *Chem. Ber.* **107**, 3176 (1974).

²⁴⁴ I. F. Eckhard, R. Fielden, and L. A. Summers, *Aust. J. Chem.* **28**, 119 (1975).

earlier report where 1,2,3,4,7,8,9,10-octahydro-4,7-phenanthroline was found to be the predominant product of Raney nickel hydrogenation of 4,7-phenanthroline under pressure.²⁴⁵ Reaction conditions apparently are all-important in determining the course of hydrogenation. With 2-methyl-, 2-ethyl-, and 2-benzyl-4,7-phenanthrolines, the 5,6-dihydro product predominated. The other product was the 7,8,9,10-tetrahydro derivative resulting from the hydrogenation of the unsubstituted ring. With the 2-phenyl derivative, only the 5,6-dihydro reduction product was formed.¹⁰¹ With finely divided platinum as catalyst, 4,7-phenanthroline is hydrogenated at near atmospheric pressure. Although a mixture of products was formed, only the 1,2,3,4-tetrahydro derivative was isolated.²⁴⁶



The chemical reduction of 4,7-phenanthroline has been re-examined. With tin and hydrochloric acid, 1,2,3,4-tetrahydro-4,7-phenanthroline predominates over the 1,2,3,4,7,8,9,10-octahydro derivative, whereas with sodium in pentanol the octahydro derivative is the principal product.²⁴⁶ In the course of the structural verification of these products, it has been found²⁴⁶ that the compound previously thought²⁴⁷ to be 3,8-dioxo-1,2,3,4,7,8,9,10-octahydro-4,7-phenanthroline (49) is in fact the linear diazaanthracene isomer (50) and the derived octahydro compound reported by Smith and Yu²⁴⁸ is likewise a diazaanthracene derivative.

Ethyl 1,4-dihydro-4-methyl-1-oxo-4,7-phenanthroline-2-carboxylate is hydrogenated with palladium-charcoal to ethyl 1,4,7,8,9,10-hexahydro-4-methyl-1-oxo-4,7-phenanthroline-2-carboxylate.²³⁸

²⁴⁵ E. Ochiai and S. Kuroyanagi, *J. Pharm. Soc. Jpn.* **63**, 213 (1943) [*CA* **45**, 5152 (1951)].

²⁴⁶ W. O. Sykes, *J. Chem. Soc.*, 4583 (1960).

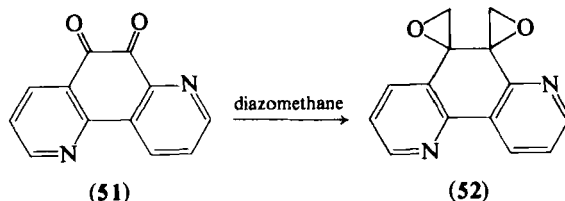
²⁴⁷ F. Mayer, L. van Zutphen, and H. Philipps, *Ber.* **60B**, 858 (1927).

²⁴⁸ P. A. S. Smith and T. Y. Yu, *J. Am. Chem. Soc.* **74**, 1096 (1952).

B. OXIDATION AND SOME OXIDATION PRODUCT REACTIONS

1. 1,7-Phenanthroline

The oxidation of 1,7-phenanthrolines containing a hydroxy, methoxy, or amino group in the 5- or 6-position to 1,7 phenanthroline-5,6-dione (**51**) by nitric acid has been patented.^{249, 250} Its monosemicarbazone has also been patented.²⁵¹ 1,7-Phenanthroline-5,6-dione (**51**) gives the diepoxide (**52**) on reaction with diazomethane.²²⁶



2. 1,8-Phenanthroline

1,8-Phenanthroline is oxidized by alkaline potassium permanganate to 2,4'-bipyridyl-3,3'-dicarboxylic acid¹⁴ and to 1,8-phenanthroline-5,6-dione in 28% yield by nitric-sulfuric acid mixtures.²⁵² The latter reaction also yielded some nitrated products and 2,5-diazafluorenone.

3. 1,10-Phenanthroline

The well documented oxidation of 1,10-phenanthroline (**4**) to 2,2'-bipyridyl-3,3'-dicarboxylic acid (**53**) by alkaline permanganate has been repeated. It is now found that 4,5-diazafluoren-9-one (**54**) is consistently a coproduct of the reaction in 20% yield.²⁵³ This provides a convenient route to this hitherto difficultly accessible compound. The formation of 4,5-diazafluoren-9-one almost certainly occurs by way of the intermediate, but not isolated, 1,10-phenanthroline-5,6-dione, which is known to undergo a benzilic acid type rearrangement in the presence of hydroxide ions to give the diazafluorenone. This rearrangement of 1,10-phenanthroline-5,6-dione has recently been studied further.¹¹⁵ Under some conditions 5,6-dihydro-5,6-dihydroxy-1,10-phenanthroline can be isolated with the diazafluorenone.

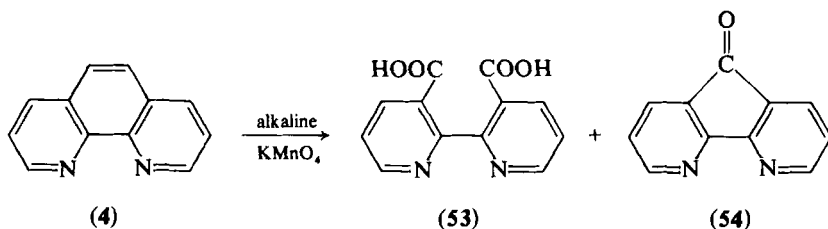
²⁴⁹ J. Druey and P. Schmidt, U.S. Patent 2,590,075 (1952) [CA 47, 149 (1953)].

²⁵⁰ Ciba Ltd., British Patent 688,802 (1953) [CA 48, 4009 (1954)].

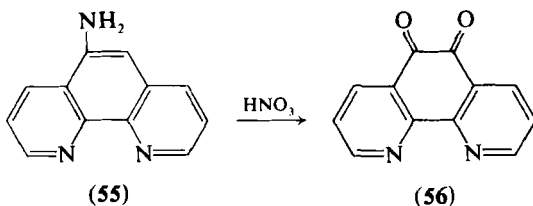
²⁵¹ Ciba Ltd., Swiss Patent 303,577 (1955) [CA 51, 1299 (1957)].

²⁵² J. Mlochowski and Z. Skrowaczewska, *Rocz. Chem.* 47, 2255 (1973).

²⁵³ I. F. Eckhard and L. A. Summers, *Aust. J. Chem.* 26, 2727 (1973).



1,10-Phenanthroline-5,6-diones are obtained by oxidation of appropriate 5-methoxy-1,10-phenanthrolines with nitric acid.^{38, 250} The parent dione (56) is also conveniently prepared in 15% overall yield from 1,10-phenanthroline via the derived 5-nitro and 5-amino (55) analogs. The latter is oxidized with nitric acid to give the dione.²⁵⁴ A related synthesis has also been reported.²⁵⁵



1,10-Phenanthroline-5,6-diones, as expected, participate in reactions typical of 1,2-diones. For example, they react with *o*-phenylenediamine to give phenazine derivatives^{38, 254} and with ethylenediamine to afford a quinoxaline.²⁵⁵

4. 4,7-Phenanthroline

Several further examples have appeared of the permanganate oxidation of 4,7-phenanthrolines to 3,3'-bipyridyl-2,2'-dicarboxylic acids.^{101, 227}

There has been considerable interest in the preparation of 4,7-phenanthroline-5,6-dione and its relatives due to their antibacterial activity. Patents^{225, 249, 250, 256, 257} have appeared covering the oxidation of 5- or 6-substituted hydroxy-, methoxy-, or amino-4,7-phenanthrolines to

²⁵⁴ J. E. Dickeson and L. A. Summers, *Aust. J. Chem.* **23**, 1023 (1970).

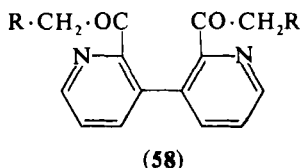
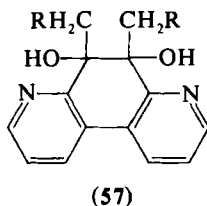
²⁵⁵ R. D. Gillard, R. E. E. Hill, and R. Maskill, *J. Chem. Soc. A*, 1447 (1970).

²⁵⁶ Ciba Ltd., French Patent 1,369,626 (1964) [CA **62**, 1664 (1965)].

²⁵⁷ Pliva Tvrnica Farmaceutskih i. Kemijskih Proizvoda, French Patent 1,382,542 (1964) [CA **63**, 7912 (1965)].

4,7-phenanthroline-5,6-dione. Similar routes to 1-methyl- and 3-methyl-4,7-phenanthroline-5,6-diones have been published²⁵⁸ and patented.^{250,259} The monosemicarbazones are also covered.^{260,261}

Reactions of 4,7-phenanthroline-5,6-dione have been the subject of considerable study. It is reduced to 5,6-dihydroxy-4,7-phenanthroline by Raney nickel hydrogenation^{226,249} or by aromatic thiols in benzene,²⁶² and oxidized by permanganate to 3,3'-bipyridyl-2,2'-dicarboxylic acid.²⁶³ It forms bishemiketals with alcohols²²⁶ and diepoxides with diazomethane.²²⁶ The diepoxides by reaction with hydrochloric acid form diols of type **57**, R = Cl, which on oxidation with lead tetraacetate give 3,3'-bipyridyl diketones of type **58**, R = Cl. Methyl ketones of type **58**, R = H, are also obtained by lead(IV) acetate oxidation of the diol **57**, R = H, obtained by lithium aluminum hydride reduction of **57**, R = Cl. With phenyldiazomethane and diphenyldiazomethane the dione forms 1,3-dioxole derivatives,^{264,265} which readily hydrolyze back to the dione with concomitant formation of benzaldehyde and benzophenone, respectively.



As a 1,2-diketone, 4,7-phenanthroline-5,6-dione reacts readily with ethylenediamine²⁵⁸ and 5,6-diamino-4,7-phenanthroline²⁶⁶ to give pyrazine derivatives. Several related condensations have also been reported.^{258,267,268} It also condenses with enamines,²⁶⁹ trialkyl and dialkyl phosphites,²⁶² and guanidine carbonate.²⁷⁰

²⁵⁸ P. Schmidt and J. Druey, *Helv. Chim. Acta* **40**, 350 (1957).

²⁵⁹ Ciba Ltd., Swiss Patent 296,573 (1954) [*CA* **50**, 5040 (1956)].

²⁶⁰ Ciba Ltd., Swiss Patent 303,576 (1955) [*CA* **51**, 1299 (1957)].

²⁶¹ J. Druey and P. Schmidt, U.S. Patent 2,755,281 (1956) [*CA* **51**, 2878 (1957)].

²⁶² M. M. Sidky and F. H. Osman, *U.A.R. J. Chem.* **14**, 225 (1971) [*CA* **77**, 139898 (1972)].

²⁶³ R. L. Williams and M. G. El Fayoumy, *J. Heterocycl. Chem.* **9**, 1021 (1972).

²⁶⁴ A. Schoenberg and G. Schuetz, *Chem. Ber.* **95**, 2386 (1962).

²⁶⁵ A. Schoenberg, E. Singer, H. Schulze-Pannier, and H. Schwarz, *Chem. Ber.* **108**, 322 (1975).

²⁶⁶ F. H. Case, *J. Heterocycl. Chem.* **4**, 157 (1967).

²⁶⁷ F. H. Case, *J. Org. Chem.* **30**, 931 (1965).

²⁶⁸ H. W. Rothkopf, D. Woehle, R. Mueller, and G. Kossmehl, *Chem. Ber.* **108**, 875 (1975).

²⁶⁹ W. Ried and E. Torok, *Liebigs Ann. Chem.* **687**, 187 (1965).

²⁷⁰ F. Feigl and D. Goldstein, *Z. Anal. Chem.* **178**, 265 (1961).

4,7-Phenanthroline-5,6-dione forms a dioxime that is advocated as a derivative suitable for its analytical estimation.²⁷¹ It reacts with β -piperidinoethoxyamine to form the corresponding monooxime, which has useful biological properties.^{272, 273}

The radical anion of 4,7-phenanthroline-5,6-dione has been prepared electrolytically, and its ESR spectrum was recorded.²⁷⁴

C. SUBSTITUTION REACTIONS

Electrophilic substitution of the electron-deficient phenanthrolines requires drastic conditions and, as predicted by theory, occurs preferentially in the benzene ring and in positions β to the nitrogen atoms. Nucleophilic substitution would be expected to proceed at sites α and γ to the nitrogen atoms.

1. 1,7-Phenanthroline

Nitration of 1,7-phenanthroline with fuming nitric acid and sulfuric acid at higher temperatures than used hitherto has improved²⁵² the yield of 6-nitro-1,7-phenanthroline to 28%. 1,5-Diazafluorenone (3%) is a by-product. Bromination of 1,7-phenanthroline in oleum gives either 6-bromo-1,7-phenanthroline or the 5,6-dibromo derivative, depending on reaction conditions.²⁷⁵

2. 1,8-Phenanthroline

Unlike 1,7-, 1,10-, and 4,7-phenanthrolines, which give nitrated products, the predominant product of the reaction of 1,8-phenanthroline (**2**) with mixed nitric and sulfuric acids is the 5,6-dione (**59**) (28%). Both the 5-nitro- (**60**) and 6-nitro-1,8-phenanthrolines (**61**) are formed, but in much lower yield (~6–7%). 2,5-Diazafluorenone (**62**) is also present (6%).²⁵² Bromination of 1,8-phenanthroline affords the 5- and 6-bromo derivatives and the 5,6-dibromo analog.²⁷⁵

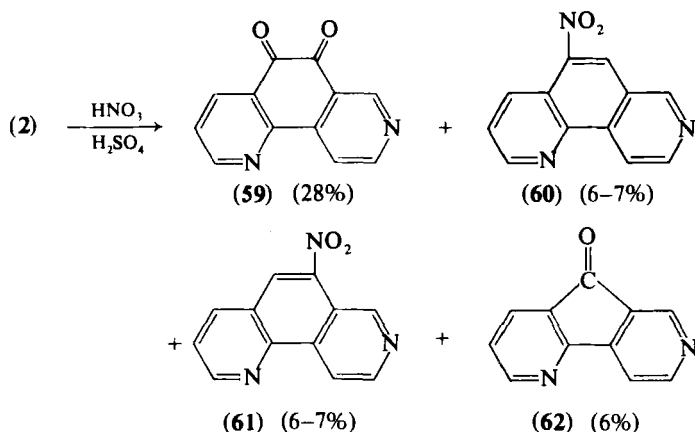
²⁷¹ I. S. Tubina and E. I. Mikhailovskaya, *Med. Prom. SSSR* **19**, 61 (1965) [*CA* **64**, 6409 (1966)].

²⁷² Ciba Ltd., British Patent 842,968 (1960) [*CA* **55**, 8434 (1961)].

²⁷³ J. Druey, K. Eichenberger, P. Schmidt, and A. Rossi, Swiss Patent 373,753 (1964) [*CA* **61**, 5615 (1964)].

²⁷⁴ A. G. Evans, J. C. Evans, and E. H. Godden, *J. Chem. Soc. B*, 149 (1970).

²⁷⁵ J. Mlochowski, *Rocz. Chem.* **48**, 2145 (1974).



3. 1,10-Phenanthroline

Reports of further studies of the nitration of 1,10-phenanthroline have appeared. Nitration with fuming nitric acid and concentrated sulfuric acid at 160°–170° gives 5-nitro-1,10-phenanthroline (75%) and 4,5-diazafluorenone (13%).²⁵²

A much milder route to 5-nitro-1,10-phenanthroline involves nitration of the tris-phenanthroline complex of cobalt(III) which is readily nitrated in concentrated sulfuric acid at 80°. The free 5-nitro-1,10-phenanthroline can be isolated in 70% yield from the nitrated complex.²⁷⁶

The first nitration of 1,10-phenanthroline in one of the pyridine rings has been accomplished by the use of fuming nitric acid in acetic anhydride.²⁵² In this way 3-nitro-1,10-phenanthroline was obtained in very low yield. The mechanism proposed for the nitration is the same as that previously proposed for the similar nitration of quinoline.²⁷⁷ 4,5-Diazafluorenone was again a coproduct.

The nitration of 1,4-dihydro-5-methoxy-2-trifluoromethyl-4-oxo-1,10-phenanthroline gives a nitrated product, presumably the 6-nitro derivative, along with the corresponding 5,6-dione.³⁸

Interest in the sulfonation of 1,10-phenanthrolines has stemmed principally from the desire to prepare water-soluble reagents for the estimation of metals. Following on from preliminary experiments on the sulfonation of 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline)²⁷⁸ and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline

²⁷⁶ A. F. Richards, J. H. Ridd, and M. L. Tobe, *Chem. Ind. (London)*, 1727 (1963).

²⁷⁷ R. D. Brown and R. D. Harcourt, *J. Chem. Soc.*, 3451 (1959).

²⁷⁸ P. Trinder, *J. Clin. Pathol.* 9, 170 (1956).

(bathocuproine),²⁷⁹ Blair and Diehl succeeded in sulfonating 1,10-phenanthroline with ammonium hydrogen sulfate at 370°. The products were 1,10-phenanthroline-3-sulfonic acid and the 5-sulfonic acid, the latter predominating. The structure of the sulfonic acids was proved by conversion into the hydroxy analogs by caustic fusion, and hence to previously prepared phenanthrolines.²⁸⁰

4,7-Diphenyl-1,10-phenanthroline and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline give disulfonic acids on reaction with chlorosulfonic acid at 25°. The position of substitution was not established, but presumably it occurs in the two phenyl rings.²⁸¹ An improved method of sulfonation utilizes hot fuming sulfuric acid.²⁸²

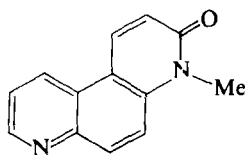
Bromination of 1,10-phenanthroline occurs in the 5- and 6-positions.²⁷⁵

Although 1,10-phenanthroline could not be induced to react with phenyl lithium, 4,7-dimethyl- and 4,7-diphenyl-1,10-phenanthrolines, as expected, afford the 4,7-dimethyl-2,9-diphenyl and 2,4,7,9-tetraphenyl derivatives, respectively.¹⁹⁶

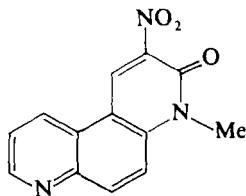
4. 4,7-Phenanthroline

Nitration of 4,7-phenanthroline has been accomplished,²⁵² thus disproving old statements that it cannot be so substituted. By using mixed nitric and sulfuric acids at 170°, a 17% yield of 5-nitro-4,7-phenanthroline was obtained. If nitric acid in acetic anhydride is used as the nitrating medium, 2-nitro-4,7-phenanthroline is the product, albeit in low yield.

The product obtained by Kaufmann and Radosevic²⁸³ by nitrating 3,4-dihydro-4-methyl-3-oxo-4,7-phenanthroline (**63**) with mixed nitric and sulfuric acids has been shown²³¹ to be the 2-nitro derivative (**64**) and not the 5-nitro derivative as previously supposed.



(63)



(64)

²⁷⁹ B. Zak, *Clin. Chim. Acta* **3**, 328 (1958).

²⁸⁰ D. E. Blair and H. Diehl, *Anal. Chem.* **33**, 867 (1961).

²⁸¹ D. Blair and H. Diehl, *Talanta* **7**, 163 (1961).

²⁸² R. L. Cryberg and H. Diehl, *Proc. Iowa Acad. Sci.* **70**, 184 (1963).

²⁸³ A. Kaufmann and R. Radosevic, *Ber.* **42**, 2612 (1909).

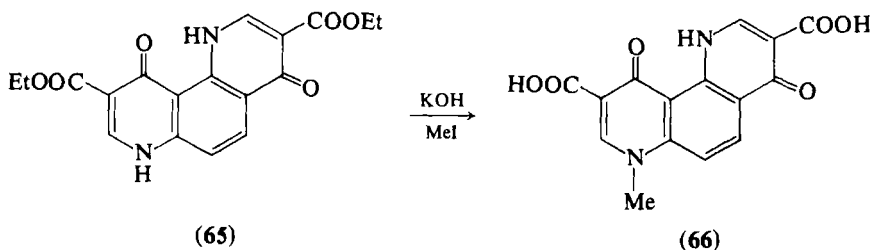
Bromination of 4,7-phenanthroline in oleum gives the 5-bromo and 5,6-dibromo derivatives, along with other dibromo and tribromo products.²⁷⁵ Attempts to sulfonate 4,7-phenanthroline have not yet succeeded.²²⁷

Reaction of 4,7-phenanthroline with aryllithiums gives the 3-aryl- and 3,8-diaryl-4,7-phenanthrolines.^{72, 284} The dihydro intermediates were isolated.

D. REACTIONS ON NITROGEN

1. 1,7-Phenanthroline

a. Quaternary Salts. Mono-quaternization of 2,8-dimethyl-1,7-phenanthroline occurs, as expected, on the easily available 7-nitrogen.²²³ 3,9-Dicarboethoxy-4,10-dihydroxy-1,7-phenanthroline, which probably exists as the 4,10-dioxo tautomer (**65**), reacts with alkaline methyl iodide to afford the *N*-methyl pyridone derivative (**66**) rather than a quaternary salt,²⁸⁵ and related compounds behave similarly.¹⁷⁵



The polarographic reduction of 1,7-phenanthroline monomethiodide has been reported.²⁸⁶ A cyanine dye has been prepared from 7,8-dimethyl-1,7-phenanthroline monomethiodide.²⁸⁷

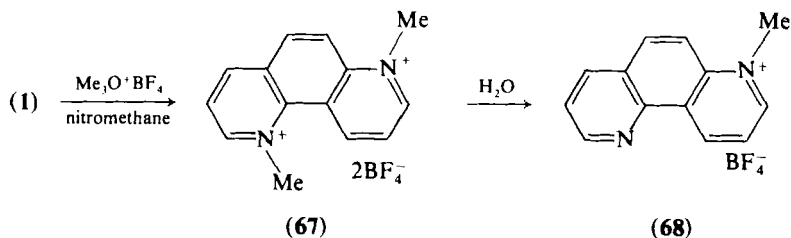
The first diquaternary salt (**67**) of 1,7-phenanthroline was prepared using trimethyloxonium fluoroborate in nitromethane.¹⁵ The salt is immediately demethylated in the 1-position in dimethyl sulfoxide, trifluoroacetic acid, or water to give **68**. If ethylene chloride is used as quaternizing solvent, the monoquaternary salt (**68**) is obtained.

²⁸⁴ H. Kato and M. Ohta, *Bull. Chem. Soc. Jpn.* **34**, 814 (1961).

²⁸⁵ M. Murakami, M. Takashima, and Y. Nagano, Japanese Patent 42,837 (1972) [*CA* **78**, 43293 (1973)].

²⁸⁶ S. Kato, J. Nakaya, and E. Imoto, *Rev. Polarogr.* **17**, 1 (1971).

²⁸⁷ F. G. Holliman and H. A. Schicklerling, *J. Chem. Soc.*, 914 (1951).



b. *N-Oxides*. Optimum conditions for the preparation of 1,7-phenanthroline 7-oxide and the 1,7-dioxide have been established²⁸⁸ using hydrogen peroxide in benzene and acetic acid or propionic acid solutions, and their ultraviolet spectra and dipole moments have been determined.⁶⁴

c. *Other Reactions*. A Reissert compound, 7-benzoyl-8-cyano-7,8-dihydro-1,7-phenanthroline was prepared from 1,7-phenanthroline, and its mass spectrum was recorded.²⁸⁹

2. 1,8-Phenanthroline

a. *Quaternary Salts*. 1,8-Phenanthroline undergoes quaternization preferentially at the readily available 8-position. A 1,8-dimethyl diquaternary salt can be obtained using trimethyloxonium fluoroborate in nitromethane. Like its 1,7-phenanthroline counterpart the diquaternary salt is readily demethylated in the 1-position.¹⁵ The diquaternary salt of 1,8-phenanthroline previously reported to be inactive as a herbicide was therefore almost certainly converted into the 8-substituted monoquaternary salt before being evaluated biologically.²⁹⁰

b. *N-Oxides*. N-Oxides of 1,8-phenanthroline have been prepared using hydrogen peroxide in an organic acid. The 8-oxide and 1,8-dioxide were both obtained; monooxidation occurs exclusively in the 8-position.²⁸⁸ Their ultraviolet spectra have been measured.⁶⁴

3. 1,9-Phenanthroline

1,9-Phenanthroline is preferentially quaternized at the 9-position and gives a 1,9-dimethyl diquaternary salt with trimethyloxonium fluoroborate in nitromethane. This diquaternary salt also is readily demethylated in the 1-position.¹⁵

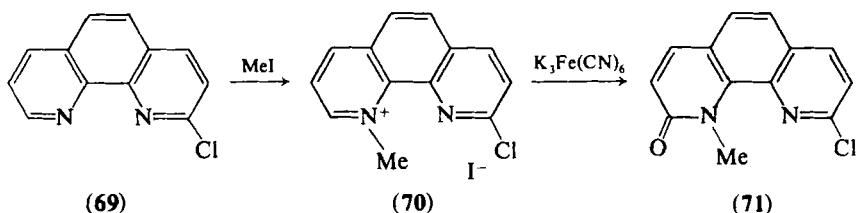
²⁸⁸ J. Mlochowski and K. Kloc, *Rocz. Chem.* **47**, 727 (1973).

²⁸⁹ F. D. Popp, K. T. Potts, and R. Armbruster, *Org. Mass. Spectrom.* **3**, 1075 (1970).

²⁹⁰ R. F. Homer, G. C. Mees, and T. E. Tomlinson, *J. Sci. Food Agr.* **11**, 309 (1960).

4. 1,10-Phenanthroline

a. *Quaternary Salts*. Several further examples have been reported of monoquaternary salts of 1,10-phenanthrolines. The parent compound forms quaternary salts with phenacyl bromides and bromoacetone.²⁹¹ Various symmetrically substituted polymethyl 1,10-phenanthrolines have been quaternized with a variety of alkyl halides.^{203,292} With unsymmetrically substituted 1,10-phenanthrolines, it is not always clear which nitrogen has been quaternized, and the structure of the products sometimes remains uncertain.^{203,292} 2-Chloro-1,10-phenanthroline (**69**), however, is quaternized in the 10-position to give (**70**), the structure of the product being proved by oxidation to 2-chloro-9,10-dihydro-10-methyl-9-oxo-1,10-phenanthroline (**71**) with potassium ferricyanide.²⁹³ A series of methyl-substituted 1-methylphenanthrolium cations has been used in an attempt to define the three-dimensional intercalation sites on DNA.²⁹⁴



4,7-Dioxo-1,4,7,10-tetrahydro-1,10-phenanthroline (**72**) with dimethyl sulfate gives 1,4-dihydro-7-methoxy-1-methyl-4-oxo-1,10-phenanthroline (**73**) rather than a quaternary salt, steric hindrance presumably preventing alkylation of both nitrogens.²⁰³ A related alkylation has also been reported.²⁹⁵ 1,2,3,4-Tetrahydro-1,10-phenanthrolines similarly form 1-alkyl derivatives rather than 10-alkyl quaternary salts with alkyl halides.³⁸ The rate of methylation of 1,10-phenanthroline with methyl iodide in dimethyl sulfoxide has been studied,²⁹⁶ and the polarographic reduction of 1-methyl-1,10-phenanthrolium iodide was reported.²⁸⁶

²⁹¹ I. C. Calder and W. H. F. Sasse, *Aust. J. Chem.* **21**, 1023 (1968).

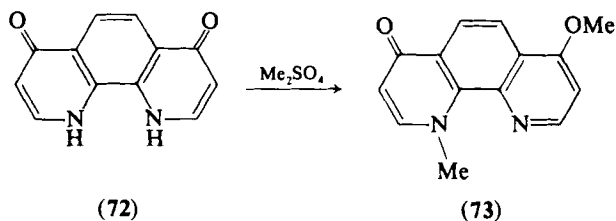
²⁹² F. P. Dwyer, R. D. Wright, and A. Shulman, Australian Patent 251,598 (1964) [*CA* **66**, 46417 (1967)].

²⁹³ S. Ogawa, T. Nakajima, and N. Gotoh, *Seisan-Kenkyu* **21**, 474 (1969) [*CA* **73**, 130913 (1970)].

²⁹⁴ E. J. Gabbay, R. E. Scofield, and C. S. Baxter, *J. Am. Chem. Soc.* **95**, 7850 (1973).

²⁹⁵ S. Minami, Y. Takase, and S. Yamabe, Japanese Patent 49,798 (1973) [*CA* **79**, 105230 (1973)].

²⁹⁶ J. A. Zoltewicz, and L. W. Deady, *J. Am. Chem. Soc.* **94**, 2765 (1972).



There has been some interest in the electrical conductivity and magnetic properties of salts of 1,10-phenanthroline and 1-alkyl-1,10-phenanthroline cations with 7,7,8,8-tetracyano-*p*-quinodimethane and its anion radical²⁹⁷⁻³⁰² and related species.³⁰³

Because of steric difficulties, it has not been found possible to obtain simple alkyl diquaternary salts of 1,10-phenanthroline. A diquaternary salt (74) of 1,10-phenanthroline is obtained, however, using 1,2-dibromoethane.³⁰⁴ 1,3-Dibromopropane, likewise, affords the salt 75.³⁰⁵ Like the analogous salts from 2,2'-bipyridyl, these salts are reduced with zinc powder in aqueous solution by a one-electron transfer not involving hydrogen to give highly colored stable radical cations of which 76, for example, is one canonical form.^{305,306} The one-electron transfer, which is almost completely reversed by air, occurs at a potential (E_0) of about -0.27 volt in aqueous solution.^{305,306} The redox properties of these salts have also been studied in solvents other than water.^{15,307} Several similar diquaternary salts of methyl-substituted 1,10-phenanthrolines have been evaluated as herbicides related to the bipyridylum salts diquat and paraquat, and their reduction potentials were recorded.³⁰⁸ Catalytic hydrogenation of the diazepine diquaternary salt 75 results in reduction of both pyridine rings, but not the central benzene ring, to afford 77, while potassium ferricyanide oxidation gives the expected dione (78).³⁰⁹

²⁹⁷ L. R. Melby, *Can. J. Chem.* **43**, 1448 (1965).

²⁹⁸ P. Dupois and J. Neel, *C.R. Hebd. Seances Acad. Sci., Ser. C* **265**, 688 (1967).

²⁹⁹ P. Dupois, S. Flandrois, and J. Neel, *C.R. Hebd. Seances Acad. Sci., Ser. C* **269**, 1091 (1969).

³⁰⁰ D. S. Acker and D. C. Blomstrom, U.S. Patent 3,162,641 (1964) [*CA* **63**, 549 (1965)].

³⁰¹ R. Buwet, P. Dupois, J. Neel, and J. Perichon, *Bull. Soc. Chim. Fr.*, 3991 (1969).

³⁰² S. Flandrois, P. Dupois, P. Delhaes, J. Amiell, and J. Neel, *J. Chim. Phys. Physicochim. Biol.* **69**, 1305 (1972) [*CA* **77**, 157985 (1972)].

³⁰³ P. Dupois and J. Neel, *C.R. Hebd. Seances Acad. Sci., Ser. C* **268**, 653 (1969).

³⁰⁴ L. A. Summers and V. A. Pickles, *Chem. Ind. (London)*, 619 (1967).

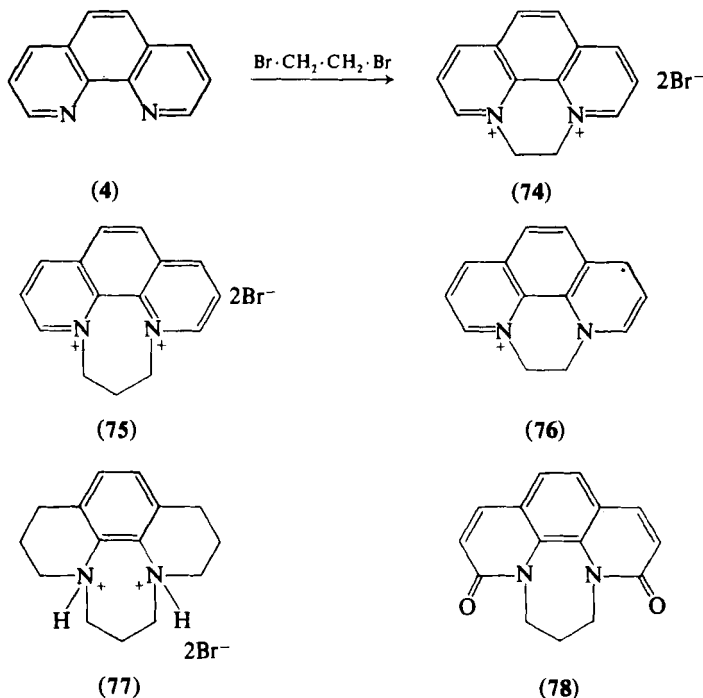
³⁰⁵ L. A. Summers, *Nature (London)* **215**, 1410 (1967).

³⁰⁶ L. A. Summers, *Tetrahedron* **24**, 5433 (1968).

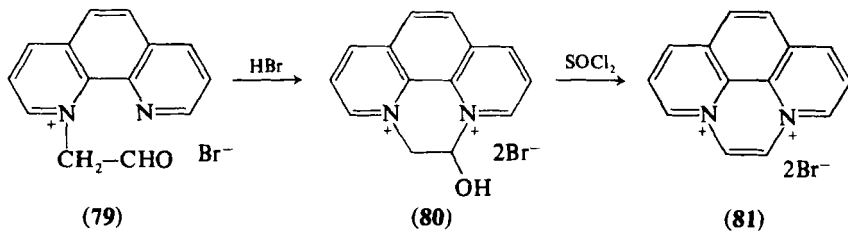
³⁰⁷ S. Hunig and J. Gross, *Tetrahedron Lett.*, 2599 (1968).

³⁰⁸ J. E. Dickeson and L. A. Summers, *J. Sci. Food Agr.* **20**, 74 (1969).

³⁰⁹ F. D. Popp and D. K. Chesney, *J. Heterocycl. Chem.* **9**, 1165 (1972).



The fully aromatic diquaternary system **81** is prepared by acid ring closure of the salt **(79)** obtained by quaternization of 1,10-phenanthroline with bromoacetaldehyde followed by dehydration of the resulting hydroxy diquaternary salt **(80)** with thionyl chloride.^{310,311} The salt **81** is unstable in aqueous solution above a pH of about 5.0. In the pH range 3.3–5.0 it is reduced by a one-electron transfer to the corresponding radical cation at a potential (E_0) of -0.12 volt.³¹¹ Its reduction in dimethylformamide solution has also been studied.^{15,307} Substituted derivatives of **81** have been prepared.³¹²



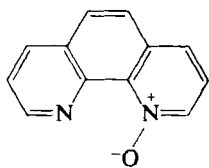
³¹⁰ A. L. Black, L. A. Summers, and V. A. Pickles, *Chem. Ind. (London)*, 1836 (1967).

³¹¹ A. L. Black and L. A. Summers, *Tetrahedron* **24**, 6453 (1968).

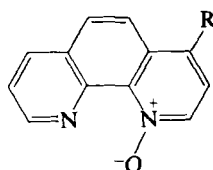
³¹² I. C. Calder and W. H. F. Sasse, *Aust. J. Chem.* **21**, 2951 (1968).

b. *N-Oxides*. Not unexpectedly, in view of steric difficulties, the claim to the preparation of 1,10-phenanthroline 1,10-dioxide³¹³ now seems to be in error. Two groups have succeeded in obtaining only the mono-*N*-oxide.^{288,314} The best yield so far recorded for the 1-oxide is the 70–80% reported by Corey and his colleagues.³¹⁵ 2-Methyl-1,10-phenanthroline gives the 2-methyl-10-oxide while 2-chloro-1,10-phenanthroline loses the chlorine group on attempted *N*-oxidation to afford 1,2-dihydro-2-oxo-1,10-phenanthroline 10-oxide.³¹⁶ The IR spectra of hydrogen halide salts of 1,10-phenanthroline 1-oxide have been studied.³¹⁷

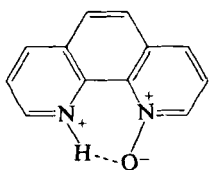
1,10-Phenanthroline 1-oxide is significantly more basic than 1,10-phenanthroline: it has a pK_a of 6.6. It reacts with benzoyl chloride and potassium cyanide to afford 2-cyano-1,10-phenanthroline, the substitution reaction taking precedence over the Reissert reaction. Contrary to previous reports, 1,10-phenanthroline 1-oxide (**82**) is nitrated, although with some difficulty, to give 4-nitro-1,10-phenanthroline 1-oxide (**83**). The nitro group is very labile and is replaced by chlorine to give (**84**) with concentrated hydrochloric acid. Both deoxygenation and replacement of the nitro group with chlorine occur when the reagent is phosphorus trichloride;³¹⁵ the product is then 4-chloro-1,10-phenanthroline (**85**). The comparative lack of activity toward electrophilic substitution is attributed to the exceptional stability of the protonated form of the 1-oxide due to hydrogen bonding (**86**). The dipole moment of the 1-oxide has been measured.⁶⁴



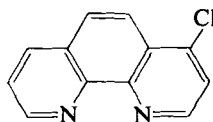
(82)

(83) R = NO₂

(84) R = Cl



(86)



(85)

³¹³ F. Linsker and R. L. Evans, *J. Am. Chem. Soc.* **68**, 403 (1946).

³¹⁴ G. Maerker and F. H. Case, *J. Am. Chem. Soc.* **80**, 2745 (1958).

³¹⁵ E. J. Corey, A. L. Borror, and T. Foglia, *J. Org. Chem.* **30**, 288 (1965).

³¹⁶ S. Ogawa and N. Gotoh, *Seisan-Kenkyu* **22**, 241 (1970) [*CA* **73**, 87818 (1970)].

³¹⁷ Z. Dega-Szafran, *Rocz. Chem.* **46**, 827 (1972).

1,10-Phenanthroline 1-oxide (**82**) is converted into the 2-deuterio derivative on treatment with NaOD-D₂O.^{317a}

5. 2,7-Phenanthroline

2,7-Phenanthroline reacts with trimethyloxonium fluoroborate in ethylene chloride solution to give the 2,7-dimethyl diquaternary salt.^{15,307} From polarography experiments it was shown to be reduced by a one-electron transfer to the corresponding radical cation. The reduction potential is lower than that of diquaternary salts of 1,10-phenanthroline, an E_0 value of -0.33 volt being recorded in aqueous solution.

6. 2,8-Phenanthroline

Crude 2,8-phenanthroline, prepared from irradiating *trans*-1-(3-pyridyl)-2-(4-pyridyl)ethylene, has been directly converted into the 2,8-dimethyl diquaternary salt with trimethyloxonium fluoroborate. This salt too is reduced by a one-electron transfer to the corresponding radical cation. The reduction potential (E_0) is -0.47 volt in aqueous solution.^{15,307}

7. 2,9-Phenanthroline

2,9-Phenanthroline reacts with trimethyloxonium fluoroborate in ethylene chloride to give the 2,9-dimethyl diquaternary salt which is reduced to the corresponding radical cation at a potential (E_0) of -0.46 volt in aqueous solution.^{15,307}

8. 3,7-Phenanthroline

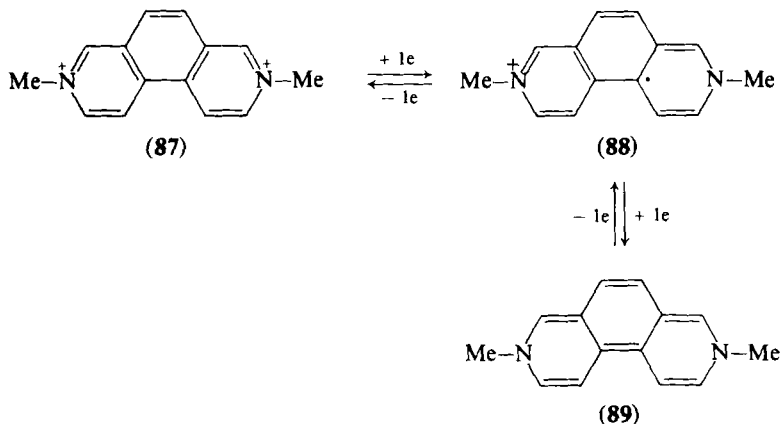
Impure 3,7-phenanthroline, obtained by the irradiation of *trans*-1-(2-pyridyl)-2-(3-pyridyl)ethylene, was converted into the 3,7-dimethyl diquaternary salt with trimethyloxonium fluoroborate. This salt is reduced to the corresponding radical cation at a potential (E_0) of -0.44 volt in aqueous solution.^{15,307}

9. 3,8-Phenanthroline

Crude 3,8-phenanthroline was likewise converted into the 3,8-dimethyl diquaternary salt with trimethyloxonium fluoroborate. The salt

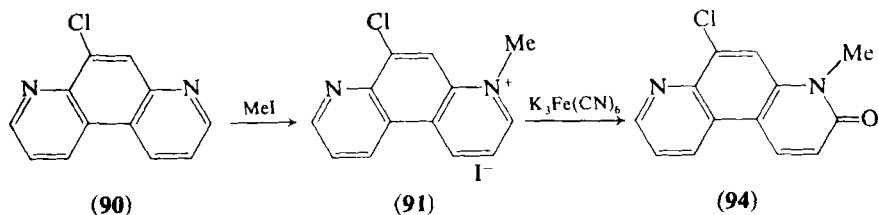
^{317a} A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *J. Chem. Soc. C*, 1193 (1971).

is reduced in aqueous solution to the corresponding radical cation at a potential (E_0) of -0.41 volt. Unlike most of the other phenanthroline diquaternary salts, this salt (**87**) behaves as a true reversible redox system, at least in dimethylformamide and acetonitrile.^{15,307} Two electrons are taken up in two distinct one-electron steps to give the radical cation **88** and the neutral molecule **89**. The salt is included in a theoretical study of redox equilibria.³¹⁸

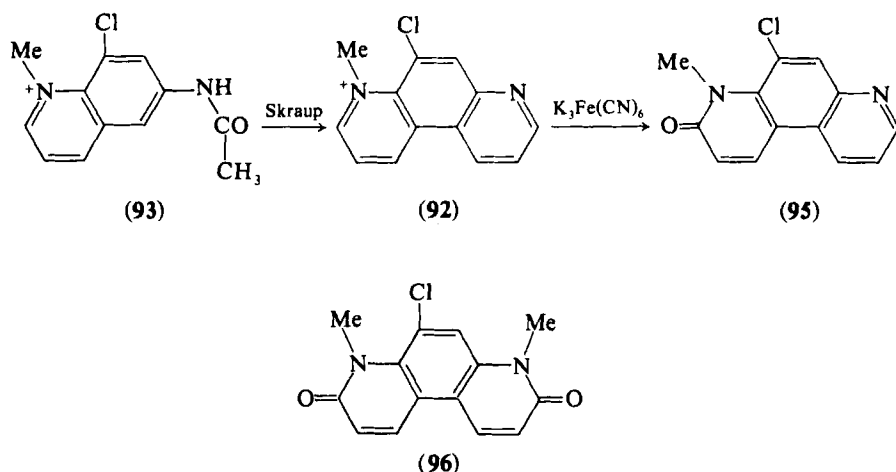


10. 4,7-Phenanthroline

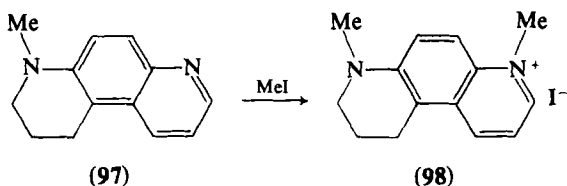
a. *Quaternary Salts.* The monoquaternary salts of 5-chloro- (**90**) and 5-bromo-4,7-phenanthrolines obtained by direct quaternization with methyl iodide have been shown²²⁷ to be 5-halogenated 7-methyl-4,7-phenanthrolium iodides (**91**), not the isomeric 4-methyl salts (**92**) which can be prepared by a Skraup reaction from the appropriate quinoline quaternary salt (**93**). Both quaternary salts **91** and **92** are oxidized with potassium ferricyanide to the corresponding oxo compounds, **94** and **95**, the quaternary methyl salts of which are both oxidized in a similar way to the same dioxo compound (**96**).



³¹⁸ P. Carsky, S. Hünig, D. Scheutzwow, and R. Zahradnik, *Tetrahedron* **25**, 4781 (1969).



By a similar sequence of reactions it has been shown²³⁰ that the monomethiodides of several 3-substituted 4,7-phenanthrolines prepared directly using methyl iodide are the 7-methyl salts and not the isomeric 4-methyl compounds as was previously thought.³¹⁹ It appears that in both the 5-substituted and 3-substituted series quaternization takes place on the less sterically hindered nitrogen atom. Sykes²²⁹ has also shown that the salt obtained by treating 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline (97) with methyl iodide is quaternized on the 7-nitrogen to give 98, not in the 4-position as described earlier.^{320, 321} 2-Carboethoxy-1,4-dihydro-1-oxo-4,7-phenanthroline is alkylated on the 4-nitrogen with alkyl halides rather than on the 7-nitrogen that would give a quaternary salt.²³⁸



Some further examples have been reported of the catalytic reduction of quaternary salts of 4,7-phenanthrolines to the corresponding tetrahydro analogs.^{229, 238} Reduction of 4-methyl-4,7-phenanthroline iodide

³¹⁹ P. Karrer and A. Pletscher, *Helv. Chim. Acta* **31**, 786 (1948).

³²⁰ P. Karrer, A. Pletscher and W. Manz, *Helv. Chim. Acta* **30**, 1146 (1947).

³²¹ P. Karrer, A. Pletscher, and W. Manz, *Helv. Chim. Acta* **31**, 1431 (1948).

with sodium borohydride is thought to give the 3,4-dihydro derivative, while the product previously³²⁰ prepared using $\text{Na}_2\text{S}_2\text{O}_4$ as reducing agent is now considered to be the corresponding 1,4-dihydro compound. Both dihydro derivatives give the same tetrahydro compound on catalytic hydrogenation.³²² The polarographic and electrochemical reduction of the salt has also been studied.^{286, 323}

Cyanine dyes have been prepared from 3,4,8-trimethyl- and 3,4,7,8-tetramethyl-4,7-phenanthroline salts.^{223, 324}

4,7-Phenanthroline methiodide reacts with phenyl magnesium bromide to give 3,4-dihydro-4-methyl-3-phenyl-4,7-phenanthroline.²⁸⁴

The 4,7-dimethyl diquatery salt of 4,7-phenanthroline is reduced in aqueous solution at a potential (E_0) of -0.30 volt by a one-electron transfer to give a radical cation. The polarographic reduction of the salt has been studied in nonaqueous solvents.^{15, 307} The electrochemical reduction of the salt has also been investigated.³²³ 4,7-Phenanthroline 4,7-dimethiodide reacts with methyl magnesium iodide to give the expected 3,4,7,8-tetrahydro-3,4,7,8-tetramethyl-4,7-phenanthroline, which is unstable in air.²⁸⁴

b. *N-Oxides*. Optimum conditions for the preparation of the 4-oxide and the 4,7-dioxide have been reported,²⁸⁸ and their ultraviolet spectra were determined.⁶⁴ 3,4-Dihydro-1-methyl-3-oxo-4,7-phenanthroline is converted into the 7-oxide with hydrogen peroxide in acetic acid. The oxide is nitrated in the 10-position. On catalytic reduction of the nitro compound 10-amino-3,4-dihydro-1-methyl-3-oxo-4,7-phenanthroline is obtained.²³²

c. *Other Reactions*. 1,2,3,4,7,8-Hexahydro-7-methyl-8-oxo-4,7-phenanthroline reacts readily with acrylonitrile, and this reaction can be used to detect small amounts of the olefin.³²⁵

E. METAL COMPLEXES OF 1,10-PHENANTHROLINE

The ability of 1,10-phenanthroline and its derivatives to form complexes with metals and nonmetals is well known. The subject has

³²² W. Traber, M. Hubmann, and P. Karrer, *Helv. Chim. Acta* **43**, 265 (1960).

³²³ S. Kato, J. Nakaya, and E. Imoto, *Rev. Polarogr.* **17**, 46 (1971) [*CA* **76**, 9782 (1972)].

³²⁴ F. A. Mikhailenko and A. N. Boguslavskaya, *Ukr. Khim. Zh.* **37**, 1031 (1971) [*CA* **76**, 60910 (1972)].

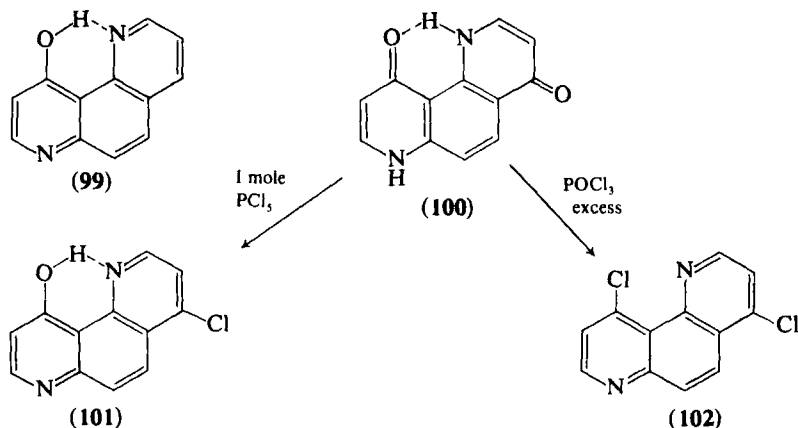
³²⁵ W. O. Sykes, *Analyst* **87**, 383 (1962).

been thoroughly reviewed.^{1, 2, 326-333} Further discussion of this topic is outside the scope of this article.

F. REACTIONS OF SUBSTITUTED PHENANTHROLINES

1. 1,7-Phenanthroline

a. *Oxo- and Hydroxy-1,7-Phenanthrolines.* 2- and 4-Hydroxypyridines normally exist in the 2-oxo and 4-oxo tautomeric forms, respectively. Hydroxyl substituents ortho and para to the ring nitrogens in phenanthrolines would therefore be expected to prefer the tautomeric oxo form. However, there are some exceptions in the 1,7-phenanthroline series. 10-Hydroxy-1,7-phenanthrolines (**99**) are often present as true hydroxy compounds owing *inter alia* to the presence of hydrogen bonding between the hydroxyl group and the nitrogen atom in the 1-position. The 4,10-dihydroxy compound, however, does probably exist as the 4,10-dione tautomer (**100**) with hydrogen bonding between the 10-oxo group and the NH group in the 1-position.^{97, 334} From IR spectral evidence it is apparent that there is also intramolecular hydrogen bonding in 6-hydroxy-1,7-phenanthroline between the 6-hydroxyl group and the 7-nitrogen.³³⁵



³²⁶ W. W. Brandt, F. P. Dwyer, and E. C. Gyarfás, *Chem. Rev.* **54**, 959 (1954).

³²⁷ L. F. Lindoy and S. E. Livingstone, *Coord. Chem. Rev.* **2**, 173 (1967).

³²⁸ E. König, *Coord. Chem. Rev.* **3**, 471 (1968).

³²⁹ F. P. Dwyer and D. P. Mellor, "Chelating Agents and Metal Chelates." Academic Press, New York, 1964.

³³⁰ S. F. Mason, *Inorg. Chim. Acta Rev.* **2**, 89 (1968).

³³¹ W. R. McWhinnie and J. D. Miller, *Adv. Inorg. Chem. Radiochem.* **12**, 135 (1969).

³³² E. D. McKenzie, *Coord. Chem. Rev.* **6**, 187 (1971).

³³³ R. D. Gillard, *Coord. Chem. Rev.* **16**, 67 (1975).

³³⁴ A. R. Surrey, A. J. Olivet, and J. O. Hoppe, *J. Am. Chem. Soc.* **76**, 4920 (1954).

³³⁵ S. F. Mason, *J. Chem. Soc.*, 4874 (1957).

There have been several further examples of the replacement of hydroxyl or oxo substituents with halogens in 1,7-phenanthrolines using phosphorus halides or oxyhalides.^{96,169-171,215} In 4,10-dioxo-1,4,7,10-tetrahydro-1,7-phenanthroline (**100**) there are marked differences in the ease with which the two oxo groups are replaced by halogen.¹⁷¹ With 1 mole of phosphorus pentachloride, the product is 4-chloro-10-hydroxy-1,7-phenanthroline (**101**). This difference in reactivity of the oxo groups is almost certainly due to the masking of the 10-oxo grouping through hydrogen bonding with the 1-nitrogen. With excess of phosphorus oxychloride the 4,10-dichloro compound **102** is obtained.

b. *Halogenated 1,7-Phenanthrolines.* As expected, halogen substituents ortho and para to the ring nitrogens in phenanthrolines are usually readily replaced by nucleophiles. Examples include replacement of the 4-chloro substituent in 4-chloro-10-hydroxy-1,7-phenanthrolines with a variety of amines^{97,171,172,334} and an ethoxyl group.⁹⁷ The chlorine group in 10-chloro-1,7-phenanthroline is similarly replaced.^{171,172}

There is a difference in the ease with which the two chlorine groups in 4,10-dichloro-1,7-phenanthroline are replaced by nucleophiles. For example, the 10-chloro substituent reacts with sodium ethoxide five hundred times faster than the 4-chloro substituent. Consequently, 4-chloro-10-ethoxy, 4-chloro-10-methoxy-, 4-chloro-10-anilino, and 4-chloro-10-hydroxy-1,7-phenanthrolines can be prepared from 4,10-dichloro-1,7-phenanthroline.^{97,171,172,336} The exceptional reactivity of the 10-chloro group is attributed to relief of strain in the transition state in its reaction with nucleophilic reagents.³³⁶ With excess of the nucleophilic reagents, both chlorines in 4,10-dichloro-1,7-phenanthroline are replaced.^{171,172,336}

Chlorine substituents may be replaced by hydrogen by reductive dehalogenation with, for example, Raney nickel or palladium-charcoal catalyst. The 1,7-phenanthroline skeleton is not reduced under these conditions.^{96,171,172} The bromine group in 4-bromo-2-trifluoromethyl-1,7-phenanthroline has been replaced by lithium and the product allowed to react with pyridine-2-aldehyde.²¹⁵

c. *Miscellaneous Substituted 1,7-Phenanthrolines.* Several further examples of the decarboxylation of carboxy-1,7-phenanthrolines have been reported.^{168,171,172,174}

5-Nitro-1,7-phenanthroline is catalytically reduced with Raney nickel to 5-amino-1,7-phenanthroline.¹⁶⁸ 4-Chloro-6-ethoxy-2-methyl-1,7-phenanthroline has been converted into the 6-hydroxy derivative with hydrobromic acid.¹⁶⁹ 4-Methyl- and 8-methyl-1,7-phenanthrolines have

³³⁶ R. A. Cutler and A. R. Surrey, *J. Am. Chem. Soc.* **77**, 2441 (1955).

been oxidized to the corresponding aldehydes with selenium dioxide,¹⁶⁶ and condensation reactions of 1,7-phenanthroline-6-aldehyde have been reported.³³⁷ 6-Methyl-1,7-phenanthroline has been converted by *N*-bromosuccinimide into 6-bromomethyl-1,7-phenanthroline, the bromine group of which has been replaced by a variety of amines.^{338,339}

2. 1,8-Phenanthroline

Only a few reports have appeared of reactions of substituted 1,8-phenanthrolines. From spectroscopic evidence it has been established that 4-hydroxy-2-trifluoromethyl-1,8-phenanthroline exists as the 4-oxo tautomer.³⁸ It is converted with phosphorus bromides into 4-bromo-2-trifluoromethyl-1,8-phenanthroline. The bromo group has been replaced by lithium with *n*-butyl lithium and the lithio derivative converted into 4-carboxy-2-trifluoromethyl-1,8-phenanthroline with carbon dioxide.²¹⁵

Chlorine groups in chloro- and dichlorobenzo[*b*][1,8]phenanthrolines have likewise been replaced by a variety of amines.¹⁸⁰

3. 1,10-Phenanthroline

a. *Oxo- and Hydroxy-1,10-Phenanthrolines*. IR spectral evidence has confirmed that 4-hydroxy-1,10-phenanthrolines exist, as expected, as the 4-oxo tautomer. They show a strong absorption at about 1630 cm⁻¹ due to the carbonyl stretching frequency and an NH absorption at about 3380 cm⁻¹.^{96,335}

Several further examples have been reported of the replacement of hydroxyl (or oxo) substituents in 1,10-phenanthrolines by halogens with phosphorus halide reagents.^{38,96,196,198,213,215,219,293,340-342} 4-Ethoxy-7-hydroxy-1,10-phenanthroline reacts normally with diazomethane to afford 4-ethoxy-7-methoxy-1,10-phenanthroline.²⁰³

b. *Halogenated 1,10-Phenanthrolines*. Halogen substituents ortho and para to the ring nitrogens in 1,10-phenanthrolines are readily replaced by nucleophiles. Several amino-substituted 1,10-phenanthrolines have been prepared from the corresponding

³³⁷ V. N. Konyukhov, G. S. Sakovich, L. V. Krupnova, and Z. V. Pushkareva, *Zh. Org. Khim.* **1**, 1487 (1965) [*CA* **64**, 6650 (1966)].

³³⁸ Z. V. Pushkareva and V. N. Konyukhov, *Zh. Obshch. Khim.* **31**, 2914 (1961) [*CA* **56**, 12868 (1962)].

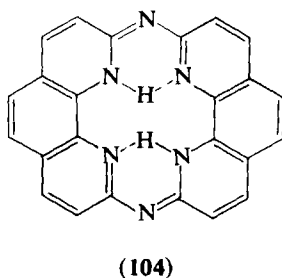
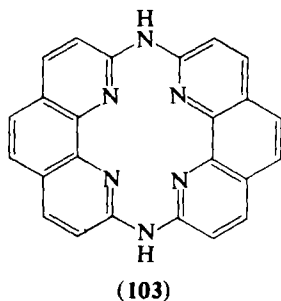
³³⁹ V. N. Konyukhov, L. N. P'yankova, and Z. V. Pushkareva, *Zh. Obshch. Khim.* **32**, 2745 (1962) [*CA* **58**, 9038 (1963)].

³⁴⁰ S. Ogawa, T. Yamaguchi, and N. Gotoh, *Chem. Commun.*, 577 (1972).

³⁴¹ S. Ogawa and N. Gotoh, *Seisan-Kenkyu* **24**, 56 (1972) [*CA* **78**, 43324 (1973)].

³⁴² C. J. Hawkins, H. Duewell, and W. F. Pickering, *Anal. Chim. Acta* **25**, 257 (1961).

halogenated compounds by reaction with amines.^{38,343} Of particular interest is the condensation of 2,9-dichloro-1,10-phenanthroline with 2,9-diamino-1,10-phenanthroline to give the macrocycle **103**. A broad absorption in the IR spectrum at 2780 cm^{-1} assigned to $\text{NH} \cdots \text{N}$ intramolecular hydrogen bonding indicates that it exists in the solid form as the tautomer **104**.^{340,344} The macrocycle has low electrical resistance.³⁴¹ 4,7-Diamino-1,10-phenanthroline is similarly prepared from 4,7-dichloro-1,10-phenanthroline by reaction with ammonia. It is stated probably to exist as an imino tautomer²⁰³ since it does not give a positive ferrioin test. With aqueous dimethylamine, 4,7-dichloro-1,10-phenanthroline gives 4-dimethylamino-7-hydroxy-1,10-phenanthroline, which does give a positive ferrioin test. Several further examples of the replacement of reactive halogen substituents in 1,10-phenanthrolines with hydroxyl or alkoxyl groups have been reported.^{38,98,203,213}



The chlorine groups in 4-chloro-1,10-phenanthroline and 4,7-dichloro-1,10-phenanthroline are replaced by cyano groups on fusion with potassium cyanide³⁴² while 2-cyano- and 5-cyano-1,10-phenanthrolines have been obtained from 2-chloro and 5-bromo-1,10-phenanthrolines, respectively, by reaction with cuprous cyanide.²⁶⁷

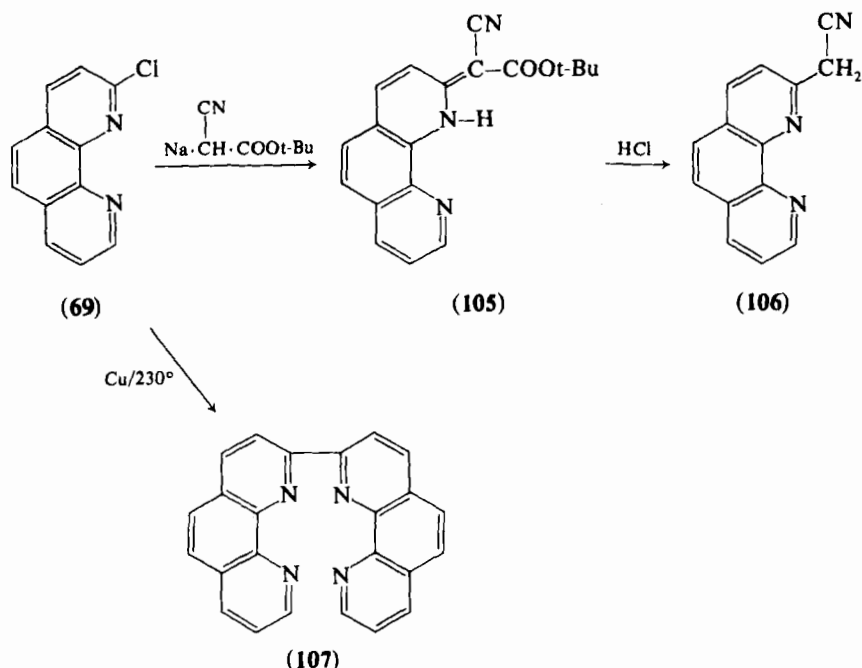
2-Chloro-1,10-phenanthroline (**69**) reacts with the sodium salt of *tert*-butyl cyanoacetate to give the intermediate **105**, which with cold hydrochloric acid affords 2-cyanomethyl-1,10-phenanthroline (**106**).³⁴⁵ 2-Chloro-1,10-phenanthroline also participates in the Ullmann reaction to afford 2,2'-bi-(1,10-phenanthroline) (**107**).³⁴⁶ 5,5'-Bi-(1,10-phenanthroline) was also prepared, but by a different route starting from 8,8'-diamino-6,6'-biquinoline.

³⁴³ S. Ogawa and N. Gotoh, *Kogyo Kagaku Zasshi* **74**, 83 (1971) [*CA* **74**, 125382 (1971)].

³⁴⁴ S. Ogawa, T. Yamaguchi, and N. Gotoh, *J. Chem. Soc. Perkin Trans. 1*, 976 (1974).

³⁴⁵ A. L. Borror and A. F. Haeberer, *J. Org. Chem.* **30**, 243 (1965).

³⁴⁶ F. H. Case, *J. Heterocycl. Chem.* **1**, 112 (1964).



Replacement of halogen substituents by hydrogen has received some attention. Catalytic dehalogenation of 7-chloro-2-methyl-1,10-phenanthroline¹⁹⁸ and 7-chlorobenzo[*b*][1,10]phenanthroline²¹⁹ with palladium-charcoal catalyst and of 4,7-dibromo-3,8-diphenyl-1,10-phenanthroline¹⁹⁶ and 4-chloro-2-methyl-1,10-phenanthroline²¹³ with Raney nickel catalyst can be accomplished without concomitant reduction of the phenanthroline rings, although frequently reduction of the ring system accompanies removal of halogen substituents.^{38, 96, 196}

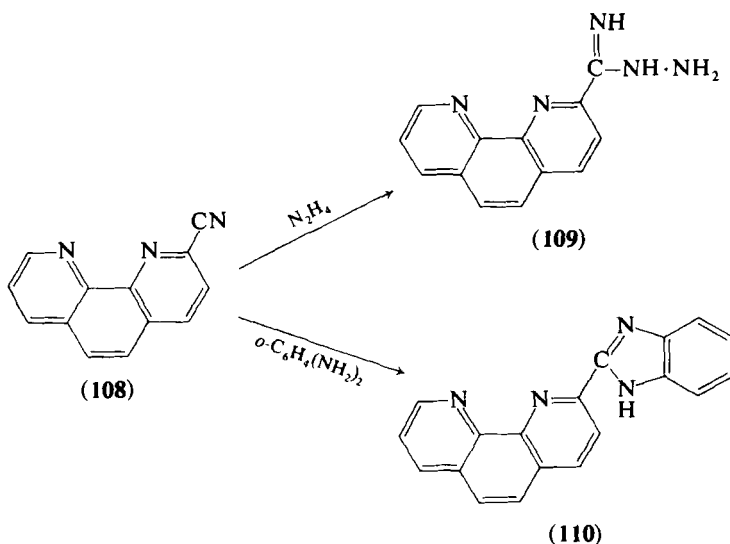
The bromine group in 4-bromo-5-methoxy-2-trifluoromethyl-1,10-phenanthroline has been replaced by lithium with *n*-butyllithium and the lithio derivative reacted with pyridine-2-aldehyde.²¹⁵

c. *Cyano-1,10-Phenanthrolines*. There has been some interest in the chemistry of cyano substituted 1,10-phenanthrolines, especially 2-cyano-1,10-phenanthroline (108). It has been used as starting material for the synthesis of several new ligands. For example, it reacts with hydrazine to afford the 2-hydrazidino derivative (109)²⁶⁷ which was subsequently utilized in the synthesis of phenanthroline-substituted triazines.^{347, 348} 2-Cyano-1,10-phenanthroline also reacts with *o*-

³⁴⁷ F. H. Case, *J. Heterocycl. Chem.* **9**, 457 (1972).

³⁴⁸ F. H. Case, *J. Heterocycl. Chem.* **10**, 353 (1973).

phenylenediamine to give a 2-substituted benzimidazole (110), and a similar reaction has been accomplished with 7,8-diaminoquinoline.²⁶⁶ 2-Cyano-1,10-phenanthroline forms 1,10-phenanthroline-2-amidoxime with hydroxylamine³⁴⁹ and the 2-carbothioamide with ammonia and subsequently hydrogen sulfide.³⁵⁰ The carbothioamide has been used for the synthesis of phenanthroline-substituted thiazoles³⁵¹ and imidazoles.³⁵²



The hydration of 2-cyano-1,10-phenanthroline to 2-carboxy-1,10-phenanthroline is strongly promoted by metals ions such as Cu^{2+} . The mechanism is thought to involve attack of external hydroxide ions on the metal complexed substrate.³⁵³

d. Miscellaneous Substituted 1,10-Phenanthrolines. 5-Nitro-1,10-phenanthroline is reduced with stannous chloride to 5-amino-1,10-phenanthroline.²¹⁹ Reduction of 5-nitro-1,10-phenanthroline with sodium borohydride gives a number of products including 5-amino-1,10-phenanthroline, *N,N'*-bis(1,10-phenanthrolin-5-yl)hydrazine and 5,5'-azo-1,10-phenanthroline, depending on reduction conditions.¹¹⁵ 5-Amino-1,10-phenanthroline forms a paramagnetic compound with the

³⁴⁹ H. A. Goodwin and F. E. Smith, *Aust. J. Chem.* **23**, 1545 (1970).

³⁵⁰ H. A. Goodwin, F. E. Smith, E. Konig, and G. Ritter, *Aust. J. Chem.* **26**, 521 (1973).

³⁵¹ H. A. Goodwin, D. W. Mather, and F. E. Smith, *Aust. J. Chem.* **28**, 33 (1975).

³⁵² D. W. Mather and H. A. Goodwin, *Aust. J. Chem.* **28**, 505 (1975).

³⁵³ R. Breslow, R. Fairweather, and J. Keana, *J. Am. Chem. Soc.* **89**, 2135 (1967).

3-carboxy-2,2,5,5-tetramethyl-3-pyrrolin-1-yloxy free radical. The compound binds to the enzyme, horse liver alcohol dehydrogenase in a 2 : 1 complex that also gives an ESR spectrum, and thus "spin labeling" of the enzyme is achieved.³⁵⁴ Diazotized 5-amino-1,10-phenanthroline has been coupled with the protein of bovine serum albumin.³⁵⁵

Further examples of the conversion of methoxy-1,10-phenanthrolines into hydroxy-1,10-phenanthrolines by the usual hydrogen halide reactions have been reported.^{98,214} 4,7-Bis-phenoxy-1,10-phenanthroline is converted into 4,7-diamino-1,10-phenanthroline by ammonium chloride at high temperatures.⁹⁸

Several reactions of 2-methyl-1,10-phenanthroline have been reported. It is readily brominated to the 2-tribromomethyl derivative, which affords 2-carboxy-1,10-phenanthroline on hydrolysis.³⁵⁶ 2-Methyl-1,10-phenanthroline reacts with aniline and sulfur to give *N*-phenyl-1,10-phenanthroline-2-carbothioamide.³⁵⁷ Oxidation of 2-methyl-phenanthrolines with selenium dioxide usually affords the 2-aldehydes,²¹³ although 2-carboxy-1,10-phenanthroline-9-aldehyde was the product isolated from the similar oxidation of 2,9-dimethyl-1,10-phenanthroline.³⁵⁸ 1,10-Phenanthroline-2-aldehyde has been condensed with aminothiols to afford phenanthroline-substituted thiazolidines useful as ligands.³⁵¹

Reduction of 1,10-phenanthroline-2-aldehyde to 1,10-phenanthroline-2-carbinol is efficiently accomplished by a dihydronicotinamide derivative in acetonitrile solution catalyzed by zinc ions. This was the first example of the reduction of an aldehyde by a NADH analog in a nonenzymic system. It also supports the catalytic function of the metal ion in the enzymic system.³⁵⁹ 1,10-Phenanthroline-2-carbinol, obtained by sodium borohydride reduction of 2-carbomethoxy-1,10-phenanthroline, is phosphorylated by adenosine triphosphate in the presence of zinc ions.³⁶⁰

Two molecules of the acid chloride of 1,10-phenanthroline-2-carboxylic acid have been condensed with a number of diamino compounds such as *o*-phenylenediamine to give novel bifunctional ligands.³⁶¹ More examples of the decarboxylation of carboxy-substituted 1,10-phenanthrolines have been described.^{98,174,198}

³⁵⁴ J. E. Spallholz and L. H. Piette, *Arch. Biochem. Biophys.* **148**, 596 (1972).

³⁵⁵ E. W. Gelewitz, W. L. Riedeman, and I. M. Klotz, *Arch. Biochem. Biophys.* **53**, 411 (1954).

³⁵⁶ H. A. Goodwin and R. N. Sylva, *Aust. J. Chem.* **20**, 217 (1967).

³⁵⁷ H. A. Goodwin, D. W. Mather, and F. E. Smith, *Aust. J. Chem.* **26**, 2623 (1973).

³⁵⁸ M. Seyhan and W. C. Fernelius, *Chem. Ber.* **91**, 469 (1958).

³⁵⁹ D. J. Creighton and D. S. Sigman, *J. Am. Chem. Soc.* **93**, 6314 (1971).

³⁶⁰ D. S. Sigman, G. M. Wahl, and D. J. Creighton, *Biochemistry* **11**, 2236 (1972).

³⁶¹ D. B. Taylor, K. P. Callahan, and I. Shaikh, *J. Med. Chem.* **18**, 1088 (1975).

4. 4,7-Phenanthroline

a. *Oxo- and Hydroxy-4,7-Phenanthrolines.* Further examples have been reported of the replacement of hydroxyl substituents in 4,7-phenanthrolines by chlorine using phosphorus oxychloride and phosphorus pentachloride. Thus, 1-methyl-3-chloro²³² and several 2-alkyl-1,3-dichloro-4,7-phenanthrolines have been prepared from the appropriate hydroxy or dihydroxy compounds.¹⁰¹

5-Hydroxy-4,7-phenanthroline is converted to 5-ethoxy-4,7-phenanthroline with ethyl bromide in alcoholic alkali solution.²²⁴

b. *Halogenated 4,7-Phenanthrolines.* More examples of the replacement of reactive halogen substituents in positions ortho and para to the ring nitrogens by nucleophiles have been reported.²³⁰ For example, the chlorine group in 8-chloro-3,4-dihydro-4-methyl-3-oxo-4,7-phenanthroline is replaced by hydrazine to give the corresponding 8-hydrazino derivative. The hydrazino group was subsequently removed by boiling aqueous copper sulfate. Less reactive chlorine substituents in the 5- or 6-positions have also been replaced but under more drastic conditions and often with the aid of a metal catalyst. Thus, 5-chloro-4,7-phenanthroline gives 5-methoxy-4,7-phenanthroline with methanolic alkali in the presence of copper.²²⁴ Likewise it forms 5-(*o*-methoxyphenoxy)-4,7-phenanthroline from reaction with guaiacol and caustic potash catalyzed by copper bronze. Replacement of 5-chloro and 5-bromo groups by amino groups with concentrated ammonia in the presence of copper acetate and phenol has also been reported.²²⁷

Reductive dehalogenation by catalytic hydrogenation of 3-chloro-,²³³ 1,3-dichloro-2-phenyl-, and 2-benzyl-1,3-dichloro-4,7-phenanthrolines can be accomplished without accompanying reduction of the 4,7-phenanthroline ring skeleton¹⁰¹ but with 1,3-dichloro-2-methyl- and 1,3-dichloro-2-ethyl-4,7-phenanthrolines mixtures of products were obtained due to concomitant reduction of the ring system.

c. *Miscellaneous Substituted 4,7-Phenanthrolines.* The *p*-toluene-sulfonyl derivative of 5-amino-4,7-phenanthroline is nitrated in the 6-position. After hydrolysis and reduction of the nitro group, 5,6-diamino-4,7-phenanthroline is obtained.²⁶⁶ Examples of the conversion of methoxy-4,7-phenanthrolines to hydroxy-4,7-phenanthrolines by the use of hydrogen halides have been reported.^{224,238} 1-Methyl-4,7-phenanthroline has been oxidized to 4,7-phenanthroline-1-aldehyde with selenium dioxide.¹⁶⁶ 3-Methyl-4,7-phenanthroline has been brominated in the side chain to afford 3-tribromomethyl-4,7-phenanthroline, which was subsequently hydrolyzed to 3-carboxy-4,7-phenanthroline.²³⁰ It also condenses with benzaldehyde to afford 3-styryl-4,7-phenanthroline

which on reaction with dilute nitric acid likewise affords the 3-carboxy derivative. Further examples of the decarboxylation of carboxy-substituted 4,7-phenanthrolines have been described.^{230, 241}

G. MISCELLANEOUS REACTIONS

1,10-Phenanthroline

The complex between 1,10-phenanthroline and picric acid was stated to be a π - π complex, not the expected n - π type.³⁶² 1,10-Phenanthroline also forms molecular complexes with phloroglucinol,³⁶³ halogenated *p*-nitrophenols;³⁶⁴ hexachlorocyclohexanes,³⁶⁵ and iodine.^{366, 367} It forms an adduct with acetic anhydride.³⁶⁸ Electronic spectra of molecular complexes of 1,10-phenanthroline with porphyrins have been recorded.³⁶⁹

The products of the thermal decomposition of 1,10-phenanthroline have been briefly discussed.³⁷⁰ Exchange of hydrogen for deuterium has been noted with alkali metal complexes of 1,10-phenanthroline. The exchange occurs principally in the 5-position.^{371, 372} A new chemiluminescence reaction arising from the combination of trichloroacetic acid and 4,7-diphenyl-1,10-phenanthroline has been reported.³⁷³

V. Uses

A. BIOLOGICALLY ACTIVE PHENANTHROLINES

1. 1,7-Phenanthroline

1,7-Phenanthroline has been shown to possess antitumor properties: it is active against certain sarcoma in mice.³⁷⁴ 1,7-Phenanthroline also

³⁶² R. D. Kross and V. A. Fassel, *J. Am. Chem. Soc.* **79**, 38 (1957).

³⁶³ P. E. Verkade and M. van Leeuwen, *Rec. Trav. Chim.* **70**, 142 (1951).

³⁶⁴ B. V. Tronov and O. A. Terekhova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol* **3**, 466 (1960) [*CA* **54**, 24729 (1960)].

³⁶⁵ H. Fuerst and K. Praeger, *Chem. Techn. (Berlin)* **14**, 158 (1962) [*CA* **58**, 4434 (1963)].

³⁶⁶ A. Szent-Gyorgyi, I. Isenberg, and S. L. Baird, *Proc. Natl. Acad. Sci. U.S.A.* **46**, 1444 (1960).

³⁶⁷ M. Orban, E. Koros, and J. Grosz, *Acta Chim. (Budapest)* **78**, 277 (1973) [*CA* **80**, 26665 (1974)].

³⁶⁸ K. C. Malhotra and D. S. Katoch, *Aust. J. Chem.* **27**, 1413 (1974).

³⁶⁹ D. Mauzerall, *Biochemistry* **4**, 1801 (1965).

³⁷⁰ I. B. Johns, E. A. McElhill, and J. O. Smith, *J. Chem. Eng. Data* **7**, 277 (1962).

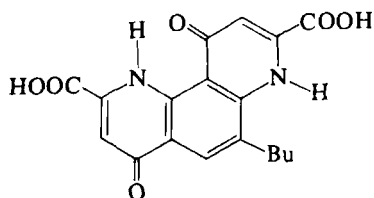
³⁷¹ M. Ishizuka and A. Ozaki, *Nippon Kagaku Kaishi* 415 (1974) [*CA* **81**, 6551 (1974)].

³⁷² T. Nakamura, M. Soma, T. Onishi, and K. Tamaru, *Z. Phys. Chem. (Frankfurt)* **89**, 122 (1974).

³⁷³ A. H. Woods and P. R. O'Bar, *Anal. Biochem.* **36**, 268 (1970).

³⁷⁴ J. Leiter, J. L. Hartwell, J. S. Kahler, I. Kline, and M. J. Shear, *J. Natl. Cancer Inst.* **14**, 365 (1953).

inhibits several enzymes.³⁷⁵⁻³⁸¹ In some cases it is suggested that the planar relatively nonpolar surfaces of phenanthrolines are responsible for this behavior. It also inhibits photosynthetic electron transport.³⁸² Several derivatives of 1,7-phenanthroline related to 8-hydroxyquinoline are biologically active. For example, 5-chloro-6-hydroxy-1,7-phenanthroline shows moderate activity against a number of micro-organisms¹⁶⁴ while 6-hydroxy-1,7-phenanthroline affects the level of blood sugar, causing hyperglycemia in rabbits.³⁸³



(111)

Dicarboxy-dihydroxy-1,7-phenanthrolines and their derivatives are useful antiasthmatic and antiallergic agents^{178,384-386} and are inhibitors of the aftereffects of the combination of antibodies and their antigens.¹⁷³ Of particular interest is 6-butyl-2,8-dicarboxy-4,10-dioxo-1,4,7,10-tetrahydro-1,7-phenanthroline (111), which has promise of being of value in treatment of human allergic conditions.³⁸⁷ 3-Carboxy-4-hydroxy-1,7-phenanthroline has been investigated as an inhibitor of various dehydrogenases³⁸⁸ while related 8-substituted analogs have been patented as

³⁷⁵ K. L. Yielding and G. M. Tomkins, *Biochim. Biophys. Acta* **62**, 327 (1962).

³⁷⁶ B. M. Anderson, M. L. Reynolds, and C. D. Anderson, *Biochim. Biophys. Acta* **113**, 235 (1966).

³⁷⁷ B. M. Anderson and M. L. Reynolds, *Arch. Biochem. Biophys.* **114**, 299 (1966).

³⁷⁸ B. H. Nevaldine and H. R. Levy, *Arch. Biochem. Biophys.* **119**, 293 (1967).

³⁷⁹ M. Nozaki, K. Ono, T. Nakazawa, S. Kotani, and O. Hayaishi, *J. Biol. Chem.* **243**, 2682 (1968).

³⁸⁰ F. Hirata, A. Nakazawa, M. Nozaki, and O. Hayaishi, *J. Biol. Chem.* **246**, 5882 (1971).

³⁸¹ K. Hori, T. Hashimoto, and M. Nozaki, *J. Biochem. (Tokyo)* **74**, 375 (1973).

³⁸² W. Oettmeier and R. Grewe, *Z. Naturforsch. C* **29**, 545 (1974).

³⁸³ I. Kadota and Y. Kawachi, *Proc. Soc. Exp. Biol. Med.* **101**, 365 (1959).

³⁸⁴ H. G. Johnson, German Patent 2,356,421 (1974) [*CA* **81**, 96448 (1974)].

³⁸⁵ C. M. Hall and H. G. Johnson, U.S. Patent 3,838,133 (1974) [*CA* **82**, 4224 (1975)].

³⁸⁶ D. P. Evans, P. W. Marshall and D. S. Thomson, *Int. Arch. Allergy Appl. Immunol.*, 417 (1975).

³⁸⁷ D. P. Evans, D. J. Gilman, D. S. Thomson, and W. S. Waring, *Nature (London)* **250**, 592 (1974).

³⁸⁸ B. R. Baker and R. R. Bramhall, *J. Med. Chem.* **15**, 235 (1972).

bactericides.^{175,389} Diquaternary salts of 4-substituted-amino-10-hydroxy-1,7-phenanthrolines are powerful neuromuscular blocking agents, the best having activity similar to that of *d*-tubocurarine.^{172,334} 1,7-Phenanthroline-5,6-dione is active against several protozoa, amoebae, and bacteria, but it is not usually as active as 4,7-phenanthroline-5,6-dione.³⁹⁰ Other derivatives of 1,7-phenanthroline have been tested for antimalarial²¹⁵ and antitumor activity¹⁶⁸ but were inactive.

2. 1,8-Phenanthroline

1,8-Phenanthroline inhibits proline incorporation into proteins.^{391,392} Benzo-substituted-1,8-phenanthrolines and 1,10-phenanthrolines are amoebicides.¹⁸⁰ 1,8-Phenanthroline-8-oxide has a wide spectrum of antibacterial activity.³⁹³

3. 1,10-Phenanthroline

There are many examples of the analytical use of 1,10-phenanthroline and its derivatives in biological systems by virtue of their chelating properties. Uses that depend solely on these properties are outside the scope of this review. The biological effects of metal complexes of 1,10-phenanthroline are also excluded. These have been reviewed.³⁹⁴

1,10-Phenanthroline and its derivatives have pronounced effect on many biological systems. The activity in many cases is due to the ability of 1,10-phenanthroline to complex with metals essential to the functioning of enzymes in living organisms. Some reports, however, indicate that factors not concerned with its ability to bind metal ions are also important.^{375, 376, 382, 395}

1,10-Phenanthroline has antitumor properties against sarcoma in mice³⁷⁴ and inhibits induction of carcinoma in rats.³⁹⁶ Quaternary salts of 6-methyl-1,10-phenanthroline are also carcinostatic.³⁹⁷

³⁸⁹ S. Minami, M. Nakata, and M. Shimizu, Japanese Patent 55,699 (1974) [*CA* 82, 156247 (1975)].

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1,10-Phenanthroline is active against many microorganisms. It is bacteriostatic and fungistatic^{393, 395, 398-405} and is a potent anthelmintic.⁴⁰⁶ It possesses tuberculostatic activity⁴⁰⁷ and is anti-spermatozoal.⁴⁰⁸ 2,9-Dimethyl-1,10-phenanthroline is even more fungistatic than the parent compound.^{398, 409} Several methyl- and phenyl-substituted 1,10-phenanthrolines and their quaternary salts are also highly active against microorganisms.^{292, 410-415} 1,10-Phenanthroline has antifibrillatory activity⁴¹⁶⁻⁴¹⁸ and inhibits gastric secretion.⁴¹⁹

1,10-Phenanthroline and its derivatives inhibit numerous enzymes.^{375-377, 379, 420-478} It inhibits respiration⁴⁷⁹⁻⁴⁸³ and has some

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⁴¹¹ Australian National University, British Patent 956,848 (1964) [*CA* **62**, 4032 (1965)].
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activity as an uncoupler of oxidative phosphorylation.⁴⁸⁴ It interferes with photosynthesis and related reactions⁴⁸⁵⁻⁵⁰⁵ and inhibits the Hill reaction.⁵⁰⁶⁻⁵⁰⁸ It has recently been suggested that the inhibition of photosynthetic electron transport by 1,10-phenanthroline is not connected with its chelating properties, since other isomeric phenanthrolines which are not chelators are also inhibitory.³⁸² Because of these properties 1,10-phenanthroline is a useful ingredient of polythene wrapping for preserving fruit during transport.⁵⁰⁹

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1,10-Phenanthrolines affect the biosynthesis of collagen^{391,392,510-514} and isoprenoids⁵¹⁵ and various metabolic processes.⁵¹⁶⁻⁵²⁰ It inhibits anaerobic fixation of nitrogen⁵²¹ and the inactivation of glucagon by microsomal membranes.⁵²²

1,10-Phenanthroline, on the other hand, stimulates the activity of some enzymes, perhaps by removing a metal that is inhibitory to the enzyme.^{523,524} It can induce porphyrin synthesis⁵²⁵ and improve the rate of ascorbate oxidation.⁵²⁶ It induces lysis of sensitized sheep erythrocytes.⁵²⁷ It is reported to reverse the resistance of microorganisms to penicillins.⁵²⁸ It binds to an immunoglobulin.⁵²⁹ It also protects rat liver from injury induced by dimethylnitrosamine⁵³⁰ and ethionine.⁵³¹

1,10-Phenanthroline has been patented as a useful enzyme inhibitor during the biological synthesis of prostaglandins.⁵³²

1,10-Phenanthroline-8-carboxylic acid derivatives have been patented as antibacterials and antifungal agents.^{295, 533-535} 1,10-Phenanthroline

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⁵³² R. Aries, French Patent 2,216,259 (1974) [*CA* **82**, 155542 (1975)].

⁵³³ T. Seki, H. Nagafusa, C. Yokoo, T. Kuribayashi, and S. Machida, Japanese Patent 35,398 (1974) [*CA* **81**, 120597 (1974)].

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5,6-dione is amoebicidal, but it is not as potent as the 4,7-phenanthroline analog.³⁹⁰ Diquaternary salts of 1,10-phenanthrolines are herbicides, but they are much less active than the 2,2'-bipyridyl analog diquat.^{305, 306, 308} Other derivatives of 1,10-phenanthroline have been patented as herbicides.²⁰⁹

4. 2,7-Phenanthroline

2,7-Phenanthroline has been reported to inhibit proline incorporation into proteins.³⁹¹

5. 4,7-Phenanthroline

4,7-Phenanthroline like 1,10- and 1,7-phenanthrolines has anticancer properties.³⁷⁴ The toxic effects of phalloidine, an isolate of the fungus *Amanita phalloides*, are inhibited by 4,7-phenanthroline.⁵³⁶ 4,7-Phenanthroline also inhibits proline incorporation into proteins.^{391, 392} 3-Methyl-4,7-phenanthroline has been suggested as a diagnostic agent for assisting in the detection of blood in body fluids.⁵³⁷

The most important biologically active 4,7-phenanthroline is 4,7-phenanthroline-5,6-dione (**112**), known as phanquone, Entobex, which is used medicinally as an amoebicide. It is active also against bacteria, protozoa, and other parasites.³⁹⁰ Several closely related derivatives are also highly active.^{224, 250, 251, 258–261, 390, 538, 539} Phanquone is used particularly in treating amoebic dysentery and is often used in combination with other antibiotics.^{540–542} The effect of 4,7-phenanthroline-5,6-dione and its relatives on cell metabolism has been investigated.⁵⁴³ It has also been reported to be mutagenic.⁵⁴⁴

⁵³⁵ T. Seki, H. Hagafusa, T. Suzuki, C. Yokoo, Y. Watanabe, K. Nakajima, S. Machida and T. Kuribayashi, Japanese Patent 69,696 (1974) [CA **81**, 136130 (1974)].

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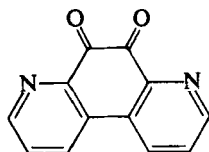
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(112)

Other derivatives of 4,7-phenanthroline have been patented as anti-bacterial and antifungal agents^{238, 272} and as antiasthmatic agents.¹⁷⁸

B. MISCELLANEOUS USES

1. 1,7-Phenanthroline

1,7-Phenanthroline has been included in a patent as an inhibitor of the polymerization of unsaturated nitriles, such as acrylonitrile.⁵⁴⁵ Because of its fluorescent properties, it has been patented for use in a luminescent electrolytic cell.^{546, 547} It has also been investigated as a coolant in nuclear reactors.^{548, 549} 6-Hydroxy-1,7-phenanthroline, as a derivative of 8-hydroxyquinoline, can be used for the spectrophotometric determination of iron(III)⁵⁵⁰ and vanadium(V).⁵⁵¹

2. 1,10-Phenanthroline

The principal use of 1,10-phenanthroline and several of its derivatives is, of course, as analytical reagents particularly for the determination of metals and in the form of their metal complexes as oxidation-reduction indicators. These uses of 1,10-phenanthrolines have been well

⁵⁴⁵ P. D. Burland, U.S. Patent 2,678,944 (1954) [CA 48, 9752 (1954)].

⁵⁴⁶ D. L. Maricle and M. M. Rauhut, Belgian Patent 666,750 (1966) [CA 65, 11769 (1966)].

⁵⁴⁷ D. L. Maricle and M. M. Rauhut, U.S. Patent 3,816,795 (1974) [CA 81, 56522 (1974)].

⁵⁴⁸ J. Weiss, C. H. Collins, J. Sucher, and N. Carciello, *Ind. Eng. Chem. Prod. Res. Develop.* 3, 73 (1964) [CA 61, 952 (1964)].

⁵⁴⁹ H. Susskind, J. Weiss, W. Becker, M. Beller, and C. H. Collins, *U.S. At. Energy Comm. BNL-7650* (1963) [CA 61, 12894 (1964)].

⁵⁵⁰ J. M. Duswalt and M. G. Mellon, *Anal. Chem.* 33, 1782 (1961).

⁵⁵¹ J. A. Dougherty and M. G. Mellon, *Anal. Chem.* 37, 1096 (1965).

⁵⁵² G. F. Smith, *Anal. Chem.* 26, 1534 (1954).

⁵⁵³ F. Vydra and M. Kopanica, *Chemist-Analyst* 52, 88 (1963).

⁵⁵⁴ G. F. Smith and F. P. Richter, "Phenanthroline and Substituted Phenanthroline Indicators." Smith Chem. Co., Columbus, Ohio, 1944.

⁵⁵⁵ H. Diehl and G. F. Smith, "The Copper Reagents-Cuproine, Neocuproine and Bathocuproine." Smith Chem. Co., Columbus, Ohio, 1958.

reviewed^{326, 552, 553} and are the subject of several booklets^{554–556} and a monograph.⁵⁵⁷ Further discussion of the analytical use of 1,10-phenanthroline and its derivatives is outside the scope of this article.

1,10-Phenanthroline in the presence of heavy metals acts as an activator of the polymerization of vinyl compounds^{558, 559} and other olefins.^{560–564} It also assists the dimerization of olefins in the presence of titanium catalysts.^{565, 566} It enhances the metal catalyzed oxidation of ascorbic acid⁵⁶⁷ and dimethyl sulfoxide.⁵⁶⁸ On the other hand, on its own it can inhibit several polymerization processes.^{545, 569} It also stabilizes butadiene and isoprene and prevents their dimerization.⁵⁷⁰ It prevents peroxide formation in ether,⁵⁷¹ inhibits the vinylation of alcohol⁵⁷² and stabilizes cumyl chloride.⁵⁷³ It accelerates the vulcanization of diene rubbers⁵⁷⁴ and copolymers.⁵⁷⁵ 1,10-Phenanthroline catalyzes the auto-oxidation of linoleic and ascorbic acids in the absence of metals.⁵⁶⁷

1,10-Phenanthroline and its metal complexes have been widely studied as promoters of the drying of various paints and coatings.^{576–584} It also prevents drying loss on aging of inks.⁵⁸⁵

⁵⁵⁶ H. Diehl and G. F. Smith, "The Iron Reagents — Bathophenanthroline, Bathophenanthroline Sulphonic Acid, 2,4,6-Tripyridyl-s-triazine, Phenyl-2-pyridyl Ketoxime." Smith Chem. Co., Columbus, Ohio, 1965.

⁵⁵⁷ A. A. Schilt, "Analytical Applications of 1,10-Phenanthroline and Related Compounds." Pergamon, New York, 1969.

⁵⁵⁸ C. A. Uranek, U.S. Patent 2,578,910 (1951) [CA 46, 3318 (1952)].

⁵⁵⁹ D. A. Rogers, U.S. Patent 2,921,873 (1960) [CA 54, 12661 (1960)].

⁵⁶⁰ H. L. Williams and J. M. Mitchell, U.S. Patent 2,631,142 (1953) [CA 47, 5159 (1953)].

⁵⁶¹ C. H. Bamford and A. N. Ferrar, *Proc. R. Soc. London, Ser. A* 321, 425 (1971).

⁵⁶² K. Kaeriyama and Y. Yamazaki, *Bull. Chem. Soc. Jpn.* 44, 3099 (1971).

⁵⁶³ K. Kaeriyama, *Nippon Kagaku Kaishi*, 813 (1972) [CA 77, 62373 (1972)].

⁵⁶⁴ S. Sugiura, S. Nakatomi, I. Makino, and T. Inoue, Japanese Patent 11,814 (1972) [CA 77, 89749 (1972)].

⁵⁶⁵ L. G. Cannell, *J. Am. Chem. Soc.* 94, 6867 (1972).

⁵⁶⁶ L. G. Cannell, *Ann. N.Y. Acad. Sci.* 214, 143 (1973).

⁵⁶⁷ E. Tanner, W. Schuler, and R. Meier, *Helv. Chim. Acta* 42, 445 (1959).

⁵⁶⁸ P. S. Radhakrishnamurti and S. C. Padhi, *Curr. Sci.* 43, 715 (1974).

⁵⁶⁹ C. H. Campbell, *J. Polym. Sci.* 32, 413 (1958).

⁵⁷⁰ H. Lauer and B. Schleppinghoff, German Patent 2,051,548 (1972) [CA 77, 76392 (1972)].

⁵⁷¹ E. Mallinckrodt and A. E. Ruehle, U.S. Patent 2,720,546 (1955) [CA 50, 7841 (1956)].

⁵⁷² S. Otsuka, Y. Matsui, and S. Murahashi *Nippon Kagaku Zasshi* 80, 1153 (1959) [CA 55, 5400 (1961)].

⁵⁷³ H. Yokoo and M. Ogawa, Japanese Patent 48,429 (1973) [CA 79, 136766 (1973)].

⁵⁷⁴ J. S. Corrigall, U.S. Patent 3,332,915 (1967) [CA 68, 3686 (1968)].

⁵⁷⁵ A. L. Barney and W. Horsberg, French Patent, 1,579,744 (1969) [CA 72, 101647 (1970)].

⁵⁷⁶ E. A. Worthington and D. G. Nicholson, *Paint, Oil, Chem. Rev.* 112, 40 (1949) [CA 43, 6836 (1949)].

1,10-Phenanthroline has been advocated as an additive for the coagulating bath in the viscose process,⁵⁸⁶ as an ingredient of the coating system for retaining fission products,⁵⁸⁷ as an antifoggant in silver halide emulsions,⁵⁸⁸ and as an ingredient of photosensitive copying material.⁵⁸⁹⁻⁵⁹² It has also been patented as a component of a polysulfide sealant mixture.⁵⁹³

1,10-Phenanthroline and some of its alkyl-substituted derivatives improve the heat stability of polyesters⁵⁹⁴ and magnetic recording tape.⁵⁹⁵ They also improve the color of cured polyester resins.⁵⁹⁶ They are also useful in various electroplating and electrolytic processes⁵⁹⁷⁻⁶⁰¹

⁵⁷⁷ G. K. Wheeler, U.S. Patent 2,526,718 (1950) [CA 45, 1358 (1951)].

⁵⁷⁸ G. K. Wheeler, U.S. Patent 2,565,897 (1951) [CA 45, 10616 (1951)].

⁵⁷⁹ A. C. Zettlemoyer and R. R. Myers, *Ind. Eng. Chem.* 46, 2220 (1954) [CA 49, 2091 (1955)].

⁵⁸⁰ W. H. Canty, G. K. Wheeler, and R. R. Myers, *Ind. Eng. Chem.* 52, 67 (1960).

⁵⁸¹ E. E. Baumhart, M. W. Kiebler, and A. Zier, U.S. Patent 2,957,786 (1960) [CA 55, 4987 (1961)].

⁵⁸² D. F. Koenecke, U.S. Patent 2,971,991 (1961) [CA 55, 12940 (1961)].

⁵⁸³ G. K. Wheeler, W. H. Canty, and R. R. Myers, *Ind. Eng. Chem., Prod. Res. Develop.* 1, 52 (1962).

⁵⁸⁴ M. Allard, *C.R. Hebd. Seances Acad. Sci., Ser. C.* 271, 42 (1970).

⁵⁸⁵ A. C. Zettlemoyer and D. M. Nace, *Ind. Eng. Chem.* 42, 491 (1950).

⁵⁸⁶ I. Kawamura, K. Yokozeki, H. Tsukioka, M. Kazushi, and S. Inoue, Japanese Patent 19,209 (1961) [CA 59, 7700 (1963)].

⁵⁸⁷ J. M. Genco, D. A. Berry, H. S. Rosenberg, G. E. Cremeans, and D. L. Morrison, *Treat. Airborne Radioactive Wastes Proc. Symp.*, 485 (1968) [CA 71, 86915 (1969)].

⁵⁸⁸ K. Matsui, T. Yamamoto, and S. Sugita, German Patent 2,013,619 (1970) [CA 74, 48059 (1971)].

⁵⁸⁹ T. Goto, K. Kojima, and S. Kusakada, Japanese Patent 5,640 (1974) [CA 80, 151151 (1974)].

⁵⁹⁰ T. Goto, K. Kojima, and S. Kusakata, Japanese Patent 1,224 (1974) [CA 81, 8386 (1974)].

⁵⁹¹ T. Goto and K. Kojima, Japanese Patent 87,330 (1974) [CA 82, 105212 (1975)].

⁵⁹² T. Goto and K. Kojima, Japanese Patent 93,018 (1974) [CA 82, 163013 (1975)].

⁵⁹³ Thiokol Chemical Corp. British Patent 984,511 (1965) [CA 62, 13390 (1965)].

⁵⁹⁴ Y. Aoki and Y. Eto, Japanese Patent 32,070 (1971) [CA 77, 62802 (1972)].

⁵⁹⁵ H. G. Ingersoll, U.S. Patent 3,585,141 (1971) [CA 75, 64980 (1971)].

⁵⁹⁶ A. Dun and D. B. Fox, U.S. Patent 3,297,788 (1967) [CA 66, 56213 (1967)].

⁵⁹⁷ Société la Verrerie Scientifique, French Patent 1,226,589 (1960) [CA 55, 17309 (1961)].

⁵⁹⁸ E. Torigai, G. Okuno, and H. Maekawa, U.S. Patent, 3,377,174 (1968) [CA 68, 116855 (1968)].

⁵⁹⁹ G. Eichkorn, F. W. Schlitter, and H. Fischer, *Ber. Bunsenges Phys. Chem.* 70, 856 (1966).

⁶⁰⁰ P. Wipper, G. Eichkorn, and H. Fischer, *Z. Metallkd.* 63, 38 (1972) [CA 76, 107208 (1972)].

⁶⁰¹ H. Hirohata and M. Oita, Japanese Patent 23,137 (1974) [CA 81, 57654 (1974)].

and enhancing conductivity in metal films.⁶⁰²⁻⁶⁰⁴ As a chelating agent 1,10-phenanthroline inhibits corrosion by cooling water.⁶⁰⁵ The use of 1,10-phenanthroline for determining the surface area of clays has been suggested,⁶⁰⁶ but the method has its limitations.⁶⁰⁷

Charge transfer complexes between various phenanthrolines and tetracyano-*p*-quinodimethane have been patented as inks and copying materials because of their high color.³⁰⁰

3. 4,7-Phenanthroline

4,7-Phenanthroline is claimed to be an inhibitor of the polymerization of unsaturated nitriles.⁵⁴⁵ Certain phenyl substituted 4,7-phenanthrolines have been patented as ultraviolet absorbing compounds for incorporation into polymers.^{608,609}

⁶⁰² H. M. McConnell, B. M. Hoffman, D. D. Thomas, and F. R. Gamble, *Proc. Natl. Acad. Sci. U.S.A.* **54**, 371 (1965).

⁶⁰³ J. Tanguy, *Thin Solid Films* **13**, 33 (1972).

⁶⁰⁴ J. Tanguy and P. Hesto, *Thin Solid Films* **21**, 129 (1974).

⁶⁰⁵ A. Weisstuch, D. A. Carter, and C. C. Nathan, *Proc. Conf. Natl. Assoc. Corros. Eng.*, **26th**, 536 (1970) [*CA* **74**, 82358 (1971)].

⁶⁰⁶ D. C. Lawrie, *Soil Sci.* **92**, 188 (1961).

⁶⁰⁷ C. A. Bower, *Soil Sci.* **95**, 192 (1963).

⁶⁰⁸ J. E. A. Otterstedt and R. Pater, U.S. Patent 3,660,404 (1972) [*CA* **77**, 48497 (1972)].

⁶⁰⁹ J. E. A. Otterstedt and R. Pater, U.S. Patent 3,812,123 (1974) [*CA* **81**, 63610 (1974)].

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Quaternization of Heteroaromatic Compounds: Quantitative Aspects

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PART I. DISCUSSION

I. Introduction

This review begins where an earlier one by Duffin¹ terminates, and it extends to the end of 1975. Apart from a few notable exceptions,²⁻⁴ the period covered by Duffin corresponds to a time when qualitative information was being obtained. Indeed, attempts to take qualitative results, such as isomer ratios based on yields of isolated products, and to use them as a basis for making statements about chemical reactivity led to incorrect conclusions.¹

The interval considered in the present survey represents a time when substantial, systematic and quantitative advances in knowledge were achieved, largely as a result of kinetic studies. However, although fresh new insight into many of the factors influencing heteroaromatic reactivity has been obtained and a solid foundation for future explorations has been laid, much remains to be done. We hope the present account will not only point out the significant progress that has been made, but also stimulate new investigations.

Our review focuses on important developments dealing with quaternization of annular nitrogen atoms of heterocyclic compounds. Only six- and five-membered heteroaromatic rings are included. The organization comprises two main parts. Part I is a comprehensive narrative describing the main electronic and steric factors of heteroaromatic

¹ G. F. Duffin, *Adv. Heterocycl. Chem.* **3**, 2 (1964).

² N. J. T. Pickles and C. N. Hinshelwood, *J. Chem. Soc.*, 1353 (1936).

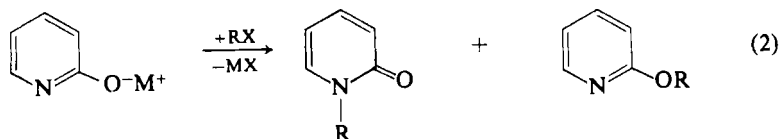
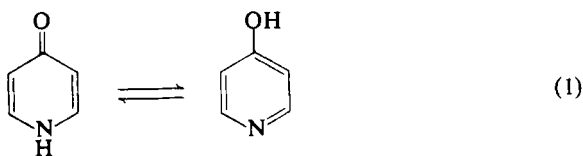
³ R. G. Pearson, S. H. Sanger, F. V. Williams, and W. J. MacGuire, *J. Am. Chem. Soc.* **74**, 5130 (1952).

⁴ H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

nucleophilic reactants that influence their reactivity. Limited consideration is given to the nature of the electrophilic alkylating agent because many general discussions dealing with such reagents in S_N2 reactions are available. Part II, not intended to be exhaustive, seeks to provide the specialist with references to recent important developments. Publications that provide little new information are generally not cited. The subject matter of Part II is organized in terms of ring structure. Cross-references are given to important information in Part I.

Six-membered rings are considered before five-membered ones because they have been studied in greater detail and consequently their reactions are better understood. Because rate constants for quaternization reactions have been correlated with pK_a values pertaining to the conjugate acids of heteroaromatic nucleophiles, substituent effects on acidities will be discussed prior to kinetic results. Acidity investigations suffer from fewer complications than N-alkylation and therefore provide results that offer considerable insight into the electronic effects of substituents on reactivity. Our review mentions only incidentally such related reactions as oxidation^{5,6} and acylation⁷ at an annular nitrogen atom.

Alkylation of "hydroxyazines" where reaction does not lead to quaternization is not considered. Molecules such as 4-pyridone usually exist largely as the carbonyl, but not as the 4-hydroxypyridine, tautomer in polar solvents⁸ [Eq. (1)]. Monoalkylation of the neutral species of such molecules can take place preferentially at either the annular nitrogen atom of the OH form or the oxygen atom of the N-H form; in each case subsequent proton loss yields a neutral product. Dialkylation then gives rise to a cationic product, the second alkyl group being introduced at the other site.



⁵ A. R. Katritzky and J. M. Lagowski, "Heteroaromatic N-Oxides." Academic Press, New York, 1970.

⁶ E. Ochial, "Aromatic N-Oxides." Elsevier, Amsterdam, 1967.

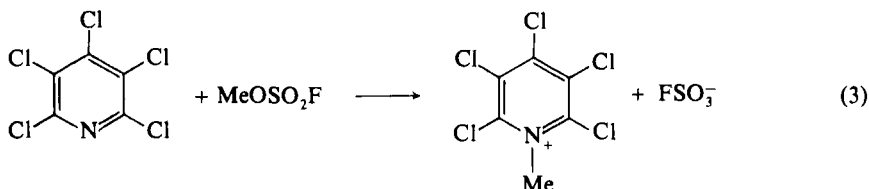
⁷ A. K. Sheinkman, S. I. Suminov, and A. N. Kost, *Russ. Chem. Rev.* **42**, 642 (1973).

⁸ P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.* **98**, 171 (1976).

Monoalkylation of salts of compounds such as 2-pyridone can give a mixture of both N- and O-alkylated material [Eq. (2)]. Solvent, metal ion, and alkylating agent can have an important influence on the product ratio.^{9,10} Considerable effort has been expended in the pyrimidine field in order to maximize yields of N-alkylated material.¹¹ Synthetic sequences involving such reactions are of great interest because they provide access to nucleosides in which a sugar group is bonded to an annular nitrogen atom.

II. Reagents for Quaternization

Quaternization of an annular nitrogen atom has been carried out with a wide range of alkylating agents. Often attached to the electrophilic carbon atom of these agents are atoms such as halogen, oxygen (oxonium salts, sulfonate, and phosphate esters^{11,12}), and less frequently nitrogen (ammonium salts¹³). Some recent examples serve as illustrations.



Alkyl fluorosulfonates are corrosive, moisture-sensitive liquids of exceptional reactivity. Weakly nucleophilic compounds, such as pentahalopyridines, are readily quaternized¹⁴ [Eq. (3)]. These reagents alkylate even the sulfur atom of thiophenes, giving high yields of products.¹⁵ But methyl fluorosulfonate will not react with 2,6-di-*tert*-butylpyridine under normal conditions, owing to steric hindrance of the nucleophilic site. In fact, the annular nitrogen atom is so hindered that it does not undergo significant hydrogen-bonding with methanol,¹⁶ and the acidity of the protonated form is abnormally high.^{17,18} However, methyl

⁹ For a discussion concerning protonation of ambident systems, see M. Liler, *Adv. Phys. Org. Chem.* **11**, 267 (1975).

¹⁰ J. P. Jonak, G. C. Hopkins, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.* **35**, 2512 (1970) and earlier references cited therein.

¹¹ K. Yamauchi and M. Kinoshita, *J. Chem. Soc., Perkin Trans. 1*, 391 (1973).

¹² Y. Yamauchi and M. Kinoshita, *J. Chem. Soc., Perkin Trans. 1*, 2506 (1973).

¹³ H. Lund and V. Lund, *Acta Chem. Scand.* **27**, 383 (1973).

¹⁴ E. Ager and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 2839 (1973).

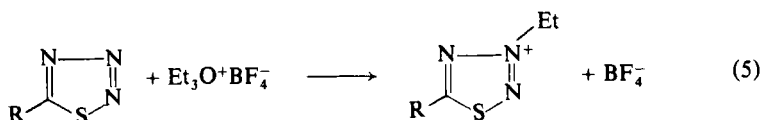
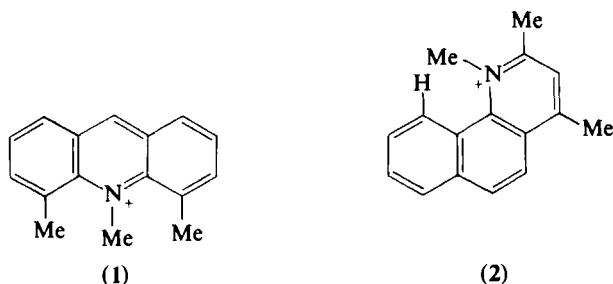
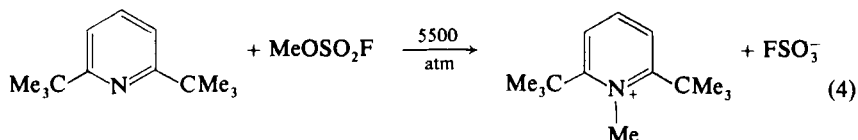
¹⁵ R. F. Heldeweg and H. Hogeveen, *Tetrahedron Lett.*, 75 (1974).

¹⁶ L. Joris and P. v. R. Schleyer, *Tetrahedron* **24**, 5991 (1968).

¹⁷ F. E. Condon, *J. Am. Chem. Soc.* **87**, 4494 (1965).

¹⁸ H. C. Brown and B. Kanner, *J. Am. Chem. Soc.* **88**, 986 (1966).

fluorosulfonate in conjunction with high pressure does produce the quaternized molecule in good yield¹⁹ [Eq. (4)]. Even under high pressure, methyl iodide (MeI) cannot be made to quaternize this pyridine in good yield, the major product being the hydroiodide formed by an α -elimination reaction of the iodide.^{19,20} Similarly, under high pressures both methyl fluorosulfonate and MeI convert the highly hindered 4,5-dimethylacridine¹⁹ and 2,4-dimethylbenzo[*h*]quinoline²¹ into their respective quaternary ions **1** and **2**.



Oxonium salts, which are moisture-sensitive solids, show high reactivity and so have been employed to quaternize weakly nucleophilic substrates, such as thiatriazoles²² [Eq. (5)]. An unusual and powerful methylating agent is heterocyclic oxonium ion **3**, which reacts with pentafluoropyridine and with the oxygen atom of ethoxybenzene.²³ Oxonium ions and fluorosulfonate esters are such powerful alkylating agents that they serve to diquaternize molecules. The two heteroatoms may be in a single ring or in adjacent rings.^{24,25} Note that examples 4–8

¹⁹ Y. Okamoto and K. I. Lee, *J. Am. Chem. Soc.* **97**, 4015 (1975).

²⁰ W. J. le Noble and Y. Ogo, *Tetrahedron* **26**, 4119 (1970).

²¹ M. L. Heffernan and I. D. Rae, unpublished observations.

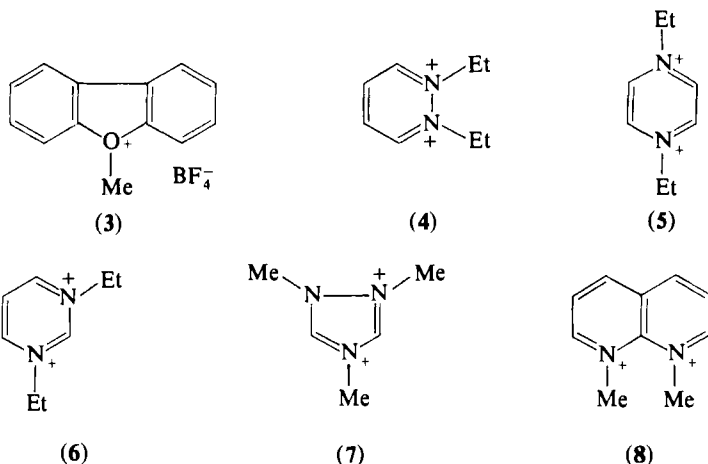
²² A. Holm, K. Schaumburg, N. Dahlberg, C. Christophersen, and J. P. Snyder, *J. Org. Chem.* **40**, 431 (1975).

²³ A. J. Copson, H. Heaney, A. A. Logun, and R. P. Sharma, *Chem. Commun.*, 315 (1972).

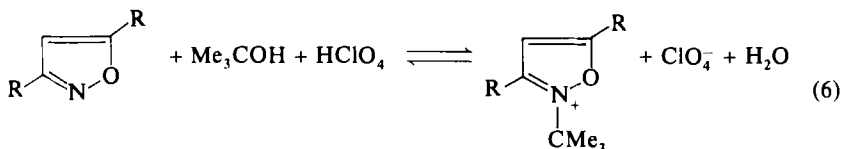
²⁴ T. J. Curphey and K. S. Prasad, *J. Org. Chem.* **37**, 2259 (1972).

²⁵ P. J. Pokorny and W. W. Paudler, *Can. J. Chem.* **51**, 476 (1973).

include both five- and six-membered rings, some having positive charges on adjacent nitrogen atoms. As expected, dications can be very reactive; some, such as the "diquat" of pyrazine, **5**, undergo spontaneous radical cation formation when placed in alcohols.²⁴ In aqueous solution, diquaternized naphthyridines such as **8** form pseudobases.^{25,26}



Usual methods employing alkylating agents to introduce a *tert*-butyl group onto an annular nitrogen atom fail because the agents undergo preferential elimination rather than substitution reactions. This limitation has been circumvented with a novel approach developed for isoxazoles. The electrophile which brings about N-alkylation is a carbonium ion produced by the reaction of an alcohol with an acid [Eq. (6)].²⁷ This quaternization reaction is reversible; increasing steric hindrance in the product disfavors its formation.²⁸ Although this approach has not been widely exploited, it is probably limited to weakly basic substrates. However, it should be noted that although reaction between 4-aminopyridines and secondary alcohols in concentrated acid does not take place at the protonated annular nitrogen atom, alkylation of the free amino group does result.²⁹



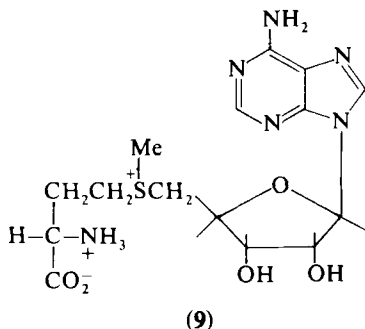
²⁶ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 962 (1974).

²⁷ R. B. Woodward and D. J. Woodman, *J. Org. Chem.* **31**, 2039 (1966).

²⁸ D. J. Woodman, *J. Org. Chem.* **33**, 2397 (1968).

²⁹ S. I. Burmistrov and A. V. Krasovskii, *Chem. Heterocycl. Compds.* **7**, 591 (1971).

Sulfonium salts are not often employed as reagents for quaternization. It is therefore interesting to note that the primary biological methylating reagent is the sulfonium salt *S*-adenosylmethionine (9).^{30,31}



III. Mechanism of Quaternization

Most quaternization reactions involving an annular nitrogen atom and an alkylating agent proceed by way of an S_N2 reaction in which inversion of configuration of a chiral reagent takes place.³² The majority of such reactions give products reflecting kinetic control. Products usually are formed irreversibly, and the ratio, when more than one material may arise, is time-independent.³³ Many approaches have been made to obtain information about the nature of the transition state of quaternization reactions, including a study of kinetic isotope effects.³⁴

One novel method, which indicates that the transition state is early, i.e., reactant-like in structure, involves the study of volume changes. Consider pyridine and MeI being converted to 1-methylpyridinium iodide. The products occupy a smaller volume than the reactants; the change, called the reaction volume, is $-46.1 \text{ cm}^3/\text{mole}$ at 25° in methanol.³⁵ The transition state for this reaction also occupies a smaller volume than the reactants; this is $-21.9 \text{ cm}^3/\text{mole}$ at 25° in acetone (activation volume).²⁰ The ratio of the activation to the reaction volume is 0.47, suggesting an early transition state. The use of two different solvents is said not to affect the comparison. Interestingly, for hindered pyridines the transition state occurs later in the reaction, the volume ratio being 0.59 and about 0.9 for 2,6-diisopropyl- and 2,6-di-*tert*-butylpyridine, respectively, reacting with MeI. In the light of these

³⁰ D. Soll, *Science* **173**, 293 (1972).

³¹ G. L. Cantoni, *Annu. Rev. Biochem.* **44**, 435 (1975).

³² K. Undheim and T. G. Gønneberg, *Acta Chem. Scand.* **25**, 18 (1971).

³³ H. Lund, *Acta Chem. Scand.* **27**, 391 (1973).

³⁴ K. T. Leffek and A. F. Matheson, *Can. J. Chem.* **50**, 982, 986 (1972).

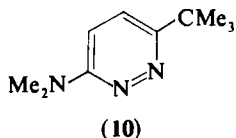
³⁵ W. J. le Noble and T. Asano, *J. Am. Chem. Soc.* **97**, 1778 (1975).

results, it is understandable that pressure-induced rate accelerations generally are greatest for the most hindered reactions.³⁶ Thus, 2,6-diisopropylpyridine reacts 38 times faster with MeI at 5000 atm than at 1 atm.²⁰ The corresponding reaction with the more hindered 2,6-di-*tert*-butylpyridine takes place at a measurable rate only at high pressure.^{19,20}

IV. Solvent Effects on Reactivity

Although enormous increases in rates of S_N2 reactions can be obtained by changing from a polar protic to a polar aprotic solvent,³⁷ such is not the case with quaternization reactions.^{38,39} Systems showing dramatic changes in reactivity involve an ionic nucleophile in contrast to quaternization reactions in which the nucleophile is uncharged. Thus, rate constants for the reaction between pyridine and benzyl chloride in methanol and in *N,N*-dimethylformamide (DMF) at 25° are nearly identical, and with benzyl bromide this same solvent change produces only at 8.8-fold rate increase. Calorimetric studies show the rate acceleration produced on passing from the hydrogen-bonding to the aprotic medium is due to a lower activation enthalpy. Solvation effects are more important for the energy of the transition state than for the reactants.⁴⁰

Because kinetic studies have been carried out employing a range of solvents, it is worthwhile to compare the magnitude of the effect of several solvents on rate constants. In keeping with a reactant-like transition state, the reactivity of pyridine toward MeI only increases by factors of 7 (25°) and 4.5 (35°) on changing from nitrobenzene⁴ to dimethyl sulfoxide (DMSO)⁴¹ and to sulfolane,⁴² respectively. Similar small changes are found with five-membered ring nucleophiles.^{43,44}



³⁶ W. J. le Noble, *Prog. Phys. Org. Chem.* **5**, 207 (1967).

³⁷ A. J. Parker, *Chem. Rev.* **69**, 1 (1969).

³⁸ M. H. Abraham, *Prog. Phys. Org. Chem.* **11**, 1 (1974).

³⁹ M. Auriel and E. de Hoffmann, *J. Am. Chem. Soc.* **97**, 7433 (1974).

⁴⁰ P. Haberfield, A. Nudelman, A. Bloom, R. Romm, and H. Ginsberg, *J. Org. Chem.* **36**, 1792 (1971).

⁴¹ J. A. Zoltewicz and L. W. Deady, *Tetrahedron* **28**, 1983 (1972).

⁴² L. W. Deady and D. C. Stillman, *Aust. J. Chem.* **29**, 1745 (1976).

⁴³ G. B. Behera, J. N. Kar, R. C. Acharya, and M. K. Rout, *J. Org. Chem.* **38**, 2164 (1973).

⁴⁴ L. W. Deady, *Aust. J. Chem.* **26**, 1949 (1973).

Solvent effects on relative rate constants are also usually small. When a heteroaromatic compound quaternizes at more than one site, for example, the product ratio can be insensitive to solvent variations. A constant isomer ratio is recorded for methylation (MeI) of 3-*tert*-butyl-6-dimethylaminopyridazine (10), in hexane, benzene, carbon tetrachloride, acetone, and acetonitrile, but not in dimethoxyethane or tetrahydrofuran. The suggestion was made that MeI may have reacted with the last two ether solvents to give an oxonium ion. Since the identity of the quaternizing agent changes, the product ratio varies as well.¹³

Other solvents also are not inert to the alkylating agent. For example, DMSO and MeI react, first (reversibly) at oxygen and then at sulfur.⁴⁵ This side-reaction becomes important only in quaternization studies involving poorly nucleophilic heteroaromatic substrates.⁴¹

V. Six-Membered Rings

A. SUBSTITUENT EFFECTS ON ACIDITIES

Substituent effects on the acidity of pyridinium ions^{46,47} have been extensively studied in order to learn about the ability of a heteroaromatic ring to transmit electronic effects and to determine how and to what extent substituents influence the protonation of an annular nitrogen atom. No other series of heteroaromatic compounds has been studied as carefully and as thoroughly as these model compounds. Yet, interpretations are far from being universally accepted. Single-parameter Hammett treatments will be considered before dual-substituent parameter (DSP) approaches.

Divergent views exist concerning the quality of correlations. One group claims that the single correlation of both 3- and 4-substituted pyridinium ion acidities with Hammett substituent constants σ_m and σ_p , [Eq. (7)] is "excellent"⁴⁸; the ρ value is 5.77. In this equation K_a and K_a^H refer to dissociation constants of substituted and unsubstituted pyridinium ions, respectively. Others suggest that the data for the 4-substituted series, considered alone, is "poorly" fitted by σ_p .⁴⁹

$$\log K_a/K_a^H = \sigma\rho \quad (7)$$

However, a more fundamental question is raised by the single-parameter correlation, regardless of opinions concerning the degree of fit using σ_p

⁴⁵ S. G. Smith and S. Winstein, *Tetrahedron* **3**, 317 (1958).

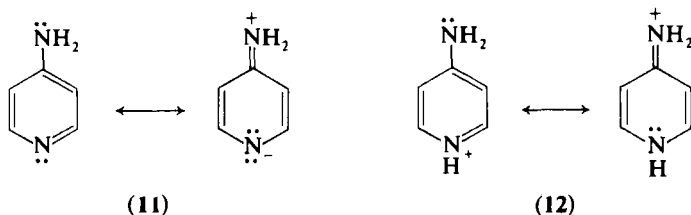
⁴⁶ A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).

⁴⁷ M. R. Chakrabarty, C. S. Handloser, and M. W. Mosher, *J. Chem. Soc., Perkin Trans. 2*, 938 (1973).

⁴⁸ H. H. Jaffé and H. L. Jones, *Adv. Heterocycl. Chem.* **3**, 209 (1964).

⁴⁹ R. W. Taft and C. A. Grob, *J. Am. Chem. Soc.* **96**, 1236 (1974).

substituent constants. It is clear that σ_p provides a superior correlation than does σ_p^+ . It is important to raise the question why this is so. Since a resonance donor substituent in the 4-position can conjugate with the positively charged nitrogen atom in a protonated form, use of a σ_p^+ -substituent parameter would seem to be appropriate. Attempts have been made to rationalize the poor correlation with σ_p^+ . Suggestions include the following: (a) There is considerable polarization in both a free base, such as 11, and its conjugate acid (12).⁴⁸ Such electron delocalization minimizes energy differences between the two forms.⁵⁰ (b) Protonation of the electron pair takes place at an orbital perpendicular to the p -orbitals of the π -system and therefore is less sensitive to effects of conjugation.⁵¹ Attempts to use other substituent constants, such as σ^0 , that diminish the resonance contribution of a substituent have limited success.⁴⁶



Notably, $\text{p}K_a$ values pertaining to solution equilibria are not usually distorted by special solvation effects. The same acidity order for 4-substituted pyridinium ions is found in the gas phase. In fact, a linear free energy (aqueous solution)–enthalpy (gas phase) relationship exists: substituent effects are 3.5 times larger in the gas phase. In other words, the aqueous solvent, relative to the gas phase, attenuates the effect of substituents by its higher dielectric constant and by hydrogen bonding.⁵²

A DSP analysis, in which contributions due to inductive and resonance effects of substituents are considered separately, has been applied in order to obtain a deeper level of insight into the electronic factors influencing pyridinium ion acidities. It has been said that a "... single parameter treatment has the merit of simplicity but where this suggests correlations which are unrealistic in terms of chemical experience, then a dual parameter approach is necessary."⁵³ The correlation has the form of Eq. (8). While only one set of inductive-effect

⁵⁰ For another point of view, see C. U. Pittman, O. M., Attallah, and L. D. Kispert, *J. Chem. Soc., Perkin Trans. 2*, 1776, (1975).

⁵¹ G. B. Ellam and C. D. Johnson, *J. Org. Chem.* **36**, 2284 (1971).

⁵² M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Am. Chem. Soc.* **94**, 1369 (1972).

⁵³ R. T. C. Brownlee and R. D. Topsom, *Tetrahedron Lett.*, 5187 (1972).

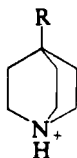
substituent constants, σ_I , is applicable, a selection must be made among four sets of resonance-effect constants.

$$\log K_a/K_a^H = \sigma_I \rho_I + \sigma_R \rho_R \quad (8)$$

Briefly, these four scales may be characterized as follows. The σ_R^0 scale gives a measure of the charge transfer abilities of substituents attached to an unperturbed π -system; σ_R (BA) values often are used for benzoic acids and derivatives. The range of values for these two scales is less than that for $\sigma_R^-(A)$ and σ_R^+ . The $\sigma_R^-(A)$ and σ_R^+ scales usually apply to series where through-conjugation is possible with a reaction center that is electron rich or poor, respectively.⁵⁴

The DSP approach nicely answers the controversial question about which substituent parameters should be employed to correlate pK_a data for 4-substituted pyridinium ions. Statistically, the best correlation is given by Eq. (9), which has σ_R^+ values to measure the resonance contribution of a substituent, a result in keeping with chemical intuition. This correlation is statistically superior to a Hammett treatment, where both resonance and inductive effects of a group are combined into a single parameter, σ_p^+ or σ_p .^{53,54} Moreover, now it is possible to rationalize why a simple Hammett treatment using σ_p works so well. Equation (9) reveals that the protonation equilibrium is much more sensitive to an inductive effect ($\rho_I = 5.15$) than to a resonance effect ($\rho_R^+ = 2.69$). Hence, substituent parameters, such as σ_p , which are derived from a consideration of the dissociation constants for benzoic acids where resonance contributions are small serve as a useful approximation. The inductive effect is said to have a larger influence on pK_a values for pyridinium ions than for benzoic acids because the distance between the substituent and the reactive site is shorter in the pyridine series.⁵³

$$\log K_a/K_a^H = 5.15\sigma_I + 2.69\sigma_R^+ \quad (4\text{-series, } 25^\circ, \text{H}_2\text{O}) \quad (9)$$



(13)

A recent report provides an alternative and elegant demonstration of the importance of enhanced resonance effects in the dissociation of 4-

⁵⁴ S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.* **10**, 1 (1973).

substituted pyridinium ions. It is found that both 4-substituted pyridinium and quinuclidinium acid (13) dissociation reactions respond in the same way to substituent inductive effects. Thus, the difference in $\log K_a/K_a^H$ between the pyridine and quinuclidine series gives a measure of the resonance effects operating in the aromatic series. An excellent correlation of this difference with σ_R^+ is found. Moreover, the results provide insight into the nature of the inductive effect. They provide support for a field over a through-bond model of inductive effects because it is unlikely that through-bond transmission effects are the same for both of these aromatic and aliphatic acids.^{54,55}

Unfortunately, the DSP treatment does not provide a definitive answer for 3-substituted pyridinium ions. There is little discrimination statistically among correlations involving σ_R^0 , $\sigma_R(\text{BA})$, or σ_R^+ to gauge resonance effects.⁵⁴ However, this limitation is not unique to these acids; other reactions involving meta-substituted compounds are known to present problems.⁵⁴ Equation (10) gives the correlation in terms of σ_R^0 values. Fortunately, the ρ value measuring the sensitivity of the series to inductive effects shows only insignificant changes as different resonance scales are considered.

$$\log K_a/K_a^H = 6.04\sigma_I + 2.63\sigma_R^0 \quad (3\text{-series}, 25^\circ, \text{H}_2\text{O}) \quad (10)$$

Acidity data for 2-substituted pyridinium ions may be correlated using a Hammett equation and σ_m values. Although it is not obvious that σ_m parameters ought to be applied to a reaction series in which a substituent and the reactive site are in an ortho relationship, the correlation clearly shows that inductive effects have an important influence on acidities.

Application of the DSP equation provides a quantitative measure of inductive and resonance contributions.⁵⁶ The data are nicely correlated by Eq. (11) which employs σ_R^+ values and shows the overwhelming importance of an inductive effect⁵⁴ for the 2-substituted series.

$$\log K_a/K_a^H = 10.60\sigma_I + 1.39\sigma_R^+ \quad (2\text{-series}, 25^\circ, \text{H}_2\text{O}) \quad (11)$$

Overall, the DSP correlations of the three sets of $\text{p}K_a$ data for pyridinium ions lead to a most interesting conclusion. The ratio of ρ values for the resonance to the inductive effect decreases from 0.52 to 0.43 to 0.13 for the 4-, 3-, and 2-series, respectively. The inductive effect increases in importance over the resonance effect as the distance between substituent and reactive site diminishes.

⁵⁵ C. A. Grob and M. G. Schlageter, *Helv. Chim. Acta* **59**, 264 (1976).

⁵⁶ M. Charton, *Prog. Phys. Org. Chem.* **8**, 235 (1971).

B. SUBSTITUENT EFFECTS ON RATES

1. *Pyridines*

a. *Sigma Value Correlations.* Three reports give results that allow an assessment of the nature of electronic effects of substituents on rates of alkylation. Although solvent and alkylating agent differ in each study, observations are very similar. Effects of substituents at a 3-position on reactivity can be correlated using a Hammett equation and σ_m substituent constants. The ρ values are moderately large and similar, being -3.13^{57} (ethyl iodide, nitrobenzene), 58 -2.53 (allyl bromide, nitromethane), 59 and -2.52^{60} (MeI, DMSO) 61,62 and show that electron-donating groups increase reactivity of a pyridine nucleophile. Modest variations in the nature of the alkylating agent and solvent do not have a large influence on the magnitude of ρ values.

Consideration of the data for 4-substituted pyridines reveals a complication. A second correlation is produced when the data are examined with the aid of Hammett's σ_p values; the ρ value is substantially smaller than that for the 3-substituted series. 48,58,59 4-Substituted compounds having electron donating groups do not react fast enough to be placed on a correlation line defined by the meta series when σ_p values are employed to estimate their electronic effects. The electron-donating effect of a para substituent is overestimated using σ_p values, but a new scale, σ^0 , of substituent parameters does give a single correlation ($\rho = -2.94$) for both meta- and para-substituted substrates. 58 Unfortunately, there is no sound chemical basis for the application of these substituent constants to the quaternization results. The σ^0 values were derived from K_a values for a reaction series having a saturated carbon atom separating the reaction site from the substituted aromatic ring. 64

Another consideration of the electronic factors influencing reactivity arises with a DSP treatment of the kinetic data; ρ values are given in

⁵⁷ This differs from the value -2.94 given in the original report 58 due to the addition of the rate constant for 3-aminopyridine.

⁵⁸ A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3596 (1964).

⁵⁹ K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).

⁶⁰ Inclusion of rate constants from Zoltewicz and Deady 61 for 3-amino-, 3-methoxy-, and 3-carbamoylpyridine changes the original value of -2.30^{62} to -2.52 ($r = 0.991$). The sigma value for the methoxy group was taken to be 0.04 rather than 0.12. 63

⁶¹ J. A. Zoltewicz and L. W. Deady, *J. Am. Chem. Soc.* **94**, 2765 (1972).

⁶² L. W. Deady and J. A. Zoltewicz, *J. Am. Chem. Soc.* **93**, 5475 (1971).

⁶³ C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.* **2**, 323 (1964).

⁶⁴ R. W. Taft, *J. Chem. Phys.* **64**, 1805 (1960).

TABLE I
CALCULATED INDUCTIVE AND RESONANCE EFFECT ρ VALUES FOR THE RATES OF
ALKYLATION OF 3- AND 4-SUBSTITUTED PYRIDINES USING $\sigma_R(\text{BA})$ AND σ_R^+
SUBSTITUENT CONSTANTS

Rxn Series	ρ_I		ρ_R		SD/RMS ^a	
	$\sigma_R(\text{BA})$	σ_R^+	$\sigma_R(\text{BA})$	σ_R^+	$\sigma_R(\text{BA})$	σ_R^+
EtI/PhNO ₂ ^b ; meta ⁵⁸	-2.81	-2.89	-1.22	-0.65	0.042	0.039
para ⁵⁸	-2.06	-2.24	-1.70	-0.94	0.129	0.092
C ₃ H ₅ Br/MeNO ₂ ; meta ⁵⁹	-2.36	-2.36	-0.80	-0.53	0.100	0.060
MeI/DMSO ^c ; meta ^{61, 62}	-2.09	-2.08	-0.86	-0.50	0.209	0.155

^a Ratio of standard deviation to root mean square of the data.

^b Values for PhCO approximated using those for MeCO.

^c CONH₂ approximated as CO₂R.

Table I. This analysis reveals that the primary effect of substituents in both the meta and para positions, as indicated by the magnitudes of these ρ values, is the inductive effect. Resonance effects are small. The situation therefore is analogous to that found in the treatment of acidities. However, the correlation method does not provide a clear distinction between two sets of resonance parameters, $\sigma_R(\text{BA})$ and σ_R^+ . The degree of fit, presented in the form of a ratio of the standard deviation (SD) to the root mean square (RMS) of the data, is similar for both resonance parameters. Perhaps this limitation reflects an early transition state in which resonance effects play a small role.

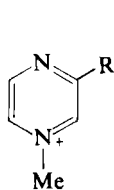
b. *Brønsted Correlations.* A Brønsted treatment successfully correlates the kinetic results for the quaternization of 3- and 4-substituted pyridines with the acidities of the corresponding conjugate acids. Although a single correlation is obtained for the 3- and 4-series, the points for 4-amino- and 4-methoxypyridines deviate from the correlation line. The amino compound is substantially less reactive, and the methoxy substrate is moderately less reactive, than expected from a consideration of $\text{p}K_a$ values.

Slopes of the correlation lines are similar for the three available sets of kinetic data.^{58, 59, 61} Because the correlation for reactions involving MeI in DMSO will be considered again, it is recorded here [Eq. (12)]. Values are slightly different from those in the original report⁶¹ owing to the inclusion of additional results (3-NH₂, 3-MeO, and 3-CONH₂ substrates⁶²; $r = 0.992$). The low value of the Brønsted slope is in keeping with the belief that the transition state occurs early in the quaternization reaction.

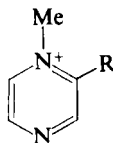
$$\log k/k^H = 0.39 \text{ p}K_a - 1.90 \quad (12)$$

2. Pyrazines

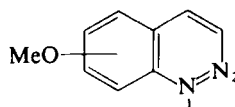
Substituent effects on reactions between monosubstituted pyrazines and MeI in DMSO are very nearly the same as those for the corresponding pyridines. Since two different annular nitrogen atoms are present in the pyrazines, isomeric products **14** and **15** may be produced. When the total rate of alkylation is corrected for the isomer content (total rate constant \times % isomer = rate constant for isomer) it is found



(14)



(15)



(16)

that a linear free-energy relationship exists involving rate constants for the formation of 3-substituted pyridinium ions and for 3-substituted pyrazinium ions (**14**). Substituent effects are slightly larger in the pyrazine series, the slope of the free-energy correlation being 1.06. Thus, the unreactive nitrogen atom acts as an independent but constant electron-withdrawing substituent.⁶² Indeed, the existence of this correlation provides unambiguous proof for the identity of the isomers produced in the alkylation reaction. This linear free-energy approach is a very powerful one and can be used in other instances to identify isomers in reactions giving rise to mixed products.

3. Fused Rings

Little is known about electronic effects of substituents in one ring influencing the reactivity of an adjacent ring. In the case of cinnolines having a methoxy group bonded to the carbocyclic rather than to the heterocyclic ring (**16**), the effect of this group on the isomer ratio is small. Quaternization always takes place largely at N-2.⁶⁵

C. STERIC EFFECTS ON RATES

1. Pyridines

a. *Ortho Alkyl Groups*. Substituents at an ortho position have long been known to hinder alkylation⁴ sterically. For reactions involving MeI

⁶⁵ D. E. Ames, H. R. Ansari, A. D. G. France, A. C. Lovesey, B. Novitt, and R. Simpson, *J. Chem. Soc. C*, 3088 (1971).

in nitrobenzene, a simple linear relationship [Eq. (13)] exists between the logarithm of relative rate constants and a steric parameter E_s for methyl, ethyl, isopropyl, and *tert*-butyl compounds, the 2-methyl compound serving as the reference substrate. The slope, δ , which is a measure of the sensitivity of the reaction series to steric effects, has the value 2.09.⁶⁶ A similar relationship is observed for reactions between 3-methyl-6-alkylpyridazines and MeI in acetonitrile. The δ -value is 1.33,⁶⁷ indicating a lower sensitivity to steric effects. The term "steric effects" is used in a broad sense and includes steric compressions, steric hindrance to solvation, as well as conformational factors.⁶⁸

$$\log k^R/k^{\text{Me}} = \delta \cdot E_s \quad (13)$$

A more subtle probe to reveal steric interactions involves the use of hydrogen and deuterium isotopes. The observations are in keeping with the idea that deuterium occupies a smaller volume than hydrogen owing to its lower zero-point energy, which gives rise to a smaller bond-stretching amplitude.^{69,70} Hence, a pyridine having a 2-CD₃ group reacts 3.0% faster with MeI than one having a 2-Me substituent. Similarly, a pyridine having two CD₃ groups at the 2,6-positions is 9.5% more reactive than the corresponding protio analog.⁷¹

Effects of methyl groups ortho to a pyridine nitrogen atom generally are not additive on rates of alkylation. Departure from additivity often becomes even greater as the size of the alkylating agent increases.⁴ Consider, for example, MeI as the alkylating agent. While the first ortho methyl group on a pyridine ring diminishes reactivity by a factor of about 2–4,^{4,59,66,72} the second retards it by 12–43.^{59,71,72}

Curiously, when liquid sulfur dioxide is used as a solvent and MeI as the quaternizing agent, one ortho methyl group retards the rate by 1% and the second by 44%.⁷³ Although nonadditivity is observed, these kinetic effects are surprisingly small.

One example does exist where the effects of ortho methyl groups are essentially additive. With ethyl methanesulfonate in water as the quaternizing agent, one methyl substituent suppresses reactivity by a factor of 2, the second by only 4.3. Moreover, the reaction is unusual in

⁶⁶ H. C. Brown and A. Cohn, *J. Am. Chem. Soc.* **77**, 1715 (1955).

⁶⁷ R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Lett.*, 3857 (1972).

⁶⁸ J. Hine, "Physical Organic Chemistry," 2nd ed. Chapter 4, McGraw-Hill, New York, 1962.

⁶⁹ P. J. Mitchell and L. Phillips, *Chem. Commun.*, 908 (1975).

⁷⁰ L. S. Bartell, *J. Am. Chem. Soc.* **83**, 3567 (1971).

⁷¹ H. C. Brown and G. J. McDonald, *J. Am. Chem. Soc.* **88**, 2514 (1966).

⁷² L. W. Deady and J. A. Zoltewicz, *J. Org. Chem.* **37**, 603 (1972).

⁷³ N. Tokura and Y. Kondo, *Bull. Chem. Soc. Jpn.* **37**, 133 (1964).

that it shows a very low Brønsted value of 0.11. Observations are rationalized in terms of a bimolecular quaternization reaction having a loose transition state⁷⁴ in which cleavage of the alkylating agent is well advanced toward products.⁷⁵

Additive effects again are not observed when interchanging the position of an alkyl group on a pyridine ring and on an alkylating agent. 2-Methylpyridine reacts 18 times slower with ethyl iodide than does 2-ethylpyridine with MeI at 25°.⁴

b. *Other Ortho Substituents.* Only one comprehensive study has been reported dealing with the quaternization of a series of 2-substituted pyridines. Results are understandable in terms of a combination of electronic and steric effects. Significantly, steric effects of NH₂, Me, Cl, Br, and CN substituents on reactivity are nearly the same. For reaction with MeI in DMSO these groups sterically retard N-methylation by an approximately constant factor of 4.2. Variations in rate constants within this series are controlled essentially by electronic effects. Since a Brønsted type of correlation ($\beta = 0.4$) is found and the acidities of the 2-substituted pyridinium ions are largely influenced by inductive effects [Eq. (11)], the electronic effects on quaternization rates for these five substrates must be largely inductive in nature as well.⁷²

Steric effects of other substituents such as Et, PhCH₂, 2-pyridyl, CO₂Me, and MeCONH are larger than those five showing the Brønsted correlation. Consequently, they cause lower reactivity. For example, the reactivities of 2-acetylamino- and 2-(2-pyridyl)pyridine are about 10 and 25 times less, respectively, than that suggested by the rate-acidity correlation for the five substrates with an approximately uniform steric impediment.⁷²

By changing the reactivity of the alkylating agent, it is possible to vary the magnitude of an ortho steric effect. Thus, the reactivity of 2-substituted pyridines toward MeI in acetone is linearly related on a logarithmic scale to the reactivity of the same substrates toward methyl fluorosulfonate in benzene. The fluorosulfonate is about 10⁴ times more reactive than the iodide, and so the transition state for quaternization occurs earlier. The earlier transition state gives rise to a smaller steric effect; the slope of the plot demonstrating the dependence of the steric effect on reactivity is 0.69.⁷⁶

⁷⁴ R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Am. Chem. Soc.* **90**, 5049 (1968).

⁷⁵ R. F. Hudson and R. J. Withey, *J. Chem. Soc.*, 3513 (1964).

⁷⁶ U. Berg, R. Gallo, J. Metzger, and M. Chanon, *J. Am. Chem. Soc.* **98**, 1260 (1976).



The effective size of a nonspherical substituent depends on the conformation it adopts during a reaction. This is well illustrated by an ortho phenyl group whose volume in a plane defined by the carbon atoms is greater than that perpendicular to this plane. Nicely illustrating the conformational dependency of the steric effect of a phenyl group are results for pyridazines. Thus, **17** is methylated 92% at N-1 and 8% at N-2. But **18** has a *tert*-butyl group adjacent to the phenyl ring causing it to rotate into a conformation where it is largely perpendicular to the heterocyclic ring, and as a consequence of the resultant smaller effective volume the product ratio is now 38% N-1 to 62% N-2.¹³

2. Ring Fusion

Fusing a benzene ring onto pyridine to give quinoline or isoquinoline gives rise to small changes in pK_a values.⁷⁷ Using a Brønsted correlation as a guide to reactivity, it can be inferred that the reactivities of the benzologs ought to be similar to that of pyridine. Indeed, the difference in reactivity between pyridine and isoquinoline is insignificant and isoquinoline does lie on a Brønsted line which includes pyridine and meta- and para-substituted pyridines.^{58,61} But quinoline deviates from this Brønsted line, largely for steric reasons. It undergoes methylation 6–9 times more slowly than pyridine.^{61,78,79} Comparison with the 2–4-fold retardation factor observed for an ortho methyl group under similar conditions reveals the smaller inhibiting effect of the methyl substituent. With quinoline, the adjacent peri center is rigidly held in a reaction plane containing the nucleophilic electron pair while a methyl group can rotate and bend away from the reaction site so as to show a smaller effect.

Steric effects on the rates of quaternization of quinoline are magnified as the size of the alkylating agent is increased in the series methyl, ethyl, and isopropyl iodide. In order to reveal the changing steric effect, it is first necessary to eliminate the reduction in rate that naturally occurs as the electrophilic carbon atom of the alkylating agent undergoes sub-

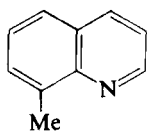
⁷⁷ D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution." Butterworth Inc., Washington, D.C., 1965.

⁷⁸ J. Packer, J. Vaughan, and E. Wong, *J. Am. Chem. Soc.* **80**, 905 (1958).

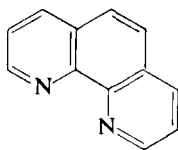
⁷⁹ R. A. Y. Jones and N. Wagstaff, *Chem. Commun.*, 56 (1969).

stitution. This may be accomplished by considering pyridine reacting with the same reagents. As the size of the alkylating agent is increased by progressive methyl substitution the rate constant for the quaternization of pyridine decreases by an essentially constant factor of 15 at 65°. But for quinoline under the same conditions the effect of the first methyl substitution is larger, being a factor of 25, and the second is larger again, 51.⁴²

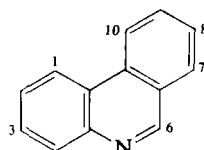
Naturally, if the volume of a peri position is increased, as in 8-methylquinoline (**19**), the steric retardation is magnified, being an enormous factor of 5780 (relative to pyridine) for a reaction with MeI in nitrobenzene.⁷⁸ However, when an annular nitrogen atom is bonded to a peri-type position as in 1,10-phenanthroline (**20**), retardation is considerably smaller. Diaza compound **20** is 2.3 and 21 times less reactive toward MeI than quinoline and pyridine, respectively. In making the comparison, data are statistically corrected for the presence of two equivalent reactive sites, but not for the weaker basicity of **20**. When the diminished basicity of **20** relative to its comparison substrates is considered, the reactivity of **20** becomes even more surprising.⁶¹ Interestingly, the rate-retarding steric effect of a second nitrogen atom is considerably less than that of a methyl group situated in the same position and is not much larger than the effect of a peri-hydrogen atom.



(19)



(20)



(21)

The rate-retarding effect on N-methylation, a factor of 33 (nitrobenzene), produced by a methyl group at position 6 of phenanthridine (**21**), is larger than the steric inhibition resulting from a methyl substituent at the equivalent 2-position of quinoline. In the quinoline case, the retardation factor is 12 (nitrobenzene)⁷⁸ or 16 (DMSO),⁶¹ depending on solvent. The greater effect in the tricyclic molecule is understandable in terms of a buttressing effect of H-7 on the adjacent ring, which inhibits the methyl group from bending away from the approaching alkylating agent.

Methyl substituents can have unusual effects on the reactivity of phenanthridine (**21**). In keeping with an electron-donating effect, the introduction of a methyl group at position 3 or 8 gives rise to a small, normal, rate acceleration in reactions with MeI. By contrast, a methyl group at position 1 or 10 produces a decrease in the rate constant for N-methylation, and methyl groups at both the 1 and 10 positions together

give rise to an increase in rate constant. Although these changes are small, it seems that the groups at positions 1 and 10 interact because of their proximity. These steric interactions produce in the normally planar aromatic molecule distortions that influence reactivity by changing the environment about the reacting annular nitrogen atom.⁸⁰ It would be interesting to employ larger groups at the remote 1- and 10-positions which might then cause larger distortions of the aromatic ring, leading to larger rate changes.

D. POLYAZINES AND ELECTRON-PAIR INTERACTIONS

Before considering compounds with two or more annular nitrogen atoms, current developments concerning the interaction of electron pairs on heteroatoms needs to be examined.⁸¹⁻⁸⁴ While it has long been recognized that unshared electron pairs on adjacent heteroatoms may interact strongly, only recently has it become clear that more widely separated electron pairs may also strongly interact. These interactions, which are transmitted both through space and through bonds, may be destabilizing as well as stabilizing. Powerful support for this concept, originally suggested by a consideration of the results of molecular orbital calculations,⁸⁵ has come from photoelectron spectroscopy.^{86,87}

An intriguing question then arises. Can evidence of the effects of pair-pair interactions be found in the solution chemistry of heterocyclic compounds in which electron transfer is not involved? Although some unusual reactivity patterns have been observed in quaternization reactions, it is not obvious that the explanation lies with pair-pair interactions.

To decide whether the reactivity of a molecule is unusual, the reactivities of reference or model substrates must be available for comparison. When considering pyridazine (**22**), pyrimidine (**23**), and pyrazine (**24**), for example, compounds having two sets of electron pairs on two annular nitrogen atoms in ortho, meta, and para arrangements, respectively, a Brønsted correlation involving substituted pyridines is a logical selection to provide comparison data. All the diazines, as well as the benzologs phthalazine (**25**) and cinnoline (**26**) (reacting at N-2) are more reactive toward MeI than predicted by a consideration of their pK_a

⁸⁰ B. R. T. Keene and G. L. Turner, *Tetrahedron* **27**, 3405 (1971).

⁸¹ N. J. Fina and J. O. Edwards, *Int. J. Chem. Kinet.* **5**, 1 (1973).

⁸² R. F. Hudson, *Angew. Chem., Int. Ed. Engl.* **12**, 36 (1973).

⁸³ G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron* **26**, 4549 (1970).

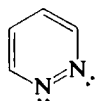
⁸⁴ J. D. Aubort, R. F. Hudson, and R. C. Woodcock, *Tetrahedron Lett.*, 2229 (1973).

⁸⁵ R. Hoffmann, *Acc. Chem. Res.* **4**, 1 (1971).

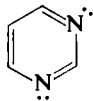
⁸⁶ A. D. Baker, *Acc. Chem. Res.* **3**, 17 (1970).

⁸⁷ R. Gleiter, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta* **55**, 255 (1972).

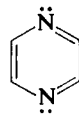
values and the Brønsted relationship. But the rate enhancements are not large, being a factor of about 3 for phthalazine, cinnoline, and pyridazine and only 38% for pyrimidine.⁶¹ Because a range of pK_a values⁷⁷ (0.5–1.1) has been reported for pyrazine, it is not possible to estimate an accurate rate enhancement factor, but it too is not large.⁶¹ Although the variation in pK_a values for the diazines has prompted a good deal of speculation,^{88, 89} it is believed that pair–pair effects do not influence equilibrium acidity values.^{81, 82}



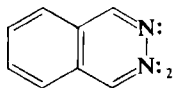
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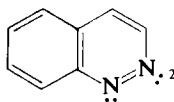
(23)



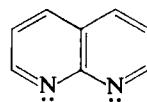
(24)



(25)



(26)



(27)

The reactivity of 1,8-naphthyridine (27) is greater than expected.^{61, 79} Here, unlike the diazines, the two heteroatoms with their unshared electron pairs are in separate rings. After correction for the two kinetically equivalent reactive sites, the rate constant for 27 is nearly the same as that for pyridine and four times larger than that for quinoline. These results are surprising, especially when it is remembered that the diaza substrate is substantially less basic than the comparison compounds. Correcting for the diminished nucleophilicity expected to be associated with the lower basicity of 27 serves to make the reactivity comparisons even more striking.⁶¹

Unfortunately, in all the examples just considered, differences between observed and predicted reactivities are not large. That there are differences between observation and prediction not only for molecules having adjacent nitrogen atoms, but also for other arrangements, is most intriguing. But larger effects must be found to be convincing. Although a more sensitive probe is found in N-acylation reactions and larger discrepancies between observed and predicted reactivities are found, only pyridazine and phthalazine are observed to possess unusually great nucleophilic properties⁶¹ whereas diazines 23 and 24 do not.⁹⁰

⁸⁸ J. Clark and D. D. Perrin, *Quart. Rev.* **18**, 295 (1964).

⁸⁹ A. Albert, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I. Chapter 1. Academic Press, New York, 1963.

⁹⁰ J. A. Zoltewicz and H. L. Jacobson, *Tetrahedron Lett.*, 189 (1972).

E. INFLUENCE OF BOND ORDER ON RATES

Although confusion has existed concerning the position (N-2) of quaternization of cinnoline (**26**), this now has been resolved.^{61,91} Clarification makes possible an interesting comparison of the reactivities of cinnoline and its isomer phthalazine (**25**). For reaction at N-2 in both compounds, phthalazine is 1.9 times as reactive as cinnoline. The enhancement in rate constants presumably reflects the different effect of benzo-fusion on bond orders in the two compounds. If the bond-order variations found in naphthalene and its monoaza derivatives^{92,93} apply to these diazanaphthalenes, then the canonical forms given by **25** and **26** represent the most important contributing structures. The double-bond character of the NN bond is greater and the internuclear distance less in cinnoline than in phthalazine. Therefore, the second nitrogen atom has a greater electron-withdrawing effect on the reactivity of the quaternizing center in cinnoline than in phthalazine.

Similarly, phthalazine is 2.3 times more reactive than pyridazine. The major factor affecting reactivity again is likely to be the difference in bond orders between the two nitrogen atoms, the greater distance between the nitrogen atoms of the benzolog giving rise to a greater reactivity. The greater basicity of phthalazine (pK_a 3.45⁷⁷) relative to pyridazine (pK_a 2.24⁷⁷) is also likely to mirror this difference in bond orders.

F. REACTIONS OF DIALKYLAMINO AND AMINO COMPOUNDS

Quaternization of dialkylamino compounds has been characterized by a number of apparently anomalous observations. Conflict often exists regarding the site of reaction, alkylation of either the annular or amino nitrogen atom being recorded. Apparent contradictions found in old reports occur because, unlike most quaternization reactions, reactions of dimethylamino-substituted nitrogen-containing heterocycles can be readily reversible. Thus, at 20°, 2-dimethylaminoquinoline (**28**) gives practically all trimethylammonio product **29**⁹⁴ resulting from quaternization of the sterically less hindered amino group, but at 100° equal amounts of this and the isomeric N(1)-methylated compound (**30**) are

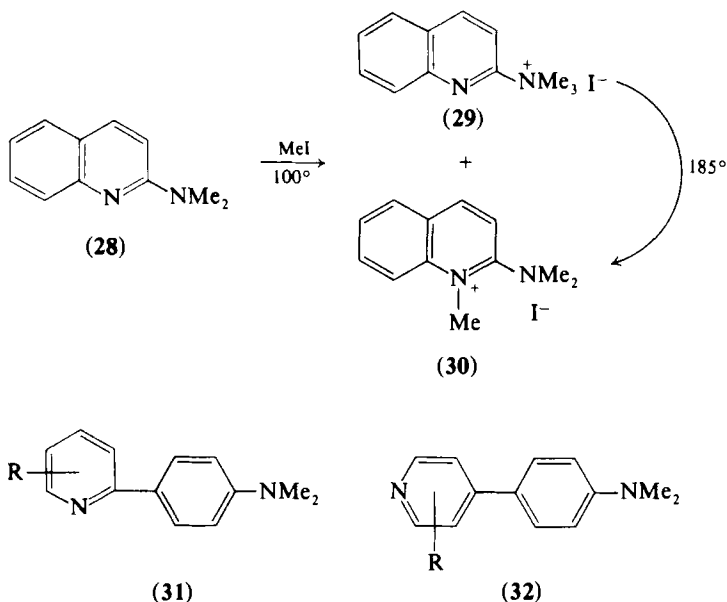
⁹¹ D. E. Ames, G. V. Boyd, A. W. Ellis, and A. C. Lovesey, *Chem. Ind. (London)*, 458 (1966).

⁹² R. Zahradnik and J. Koutecky, *Adv. Heterocycl. Chem.* **5**, 69 (1965).

⁹³ C. Sabelli, P. Tangocci, and P. F. Zanazzi, *Acta Crystallogr., Sect. B* **25**, 2231 (1969).

⁹⁴ G. B. Barlin and A. C. Young, *J. Chem. Soc., B*, 2323 (1971).

formed.⁹⁵ At 185°, the trimethylammonio product can be made to rearrange to the thermodynamically favored isomer **30**.⁹⁶ Essentially the same behavior is noted with 2-dimethylaminopyridine. Here the side-chain product is favored (9:1) at 100°, but isomerization occurs at 160°.⁹⁷



Positioning a phenylene group between a pyridine ring and a dimethylamino substituent does little to modify the pattern. Thus, **31**, which has this group located ortho to the annular nitrogen atom, quaternizes faster at the exocyclic site, but the ring-methylated product is more stable.⁹⁸ However, when the phenylene group is more remote, as in **32**, quaternization occurs at the ring nitrogen atom exclusively.⁹⁹

Apparently, the interesting and sometimes puzzling observations with amino substrates reflect competition between steric factors and electronic considerations. When an annular nitrogen atom becomes hindered, reaction takes place more easily at the amino group. However, this ammonio product often has a higher energy than that resulting from quaternization of an annular position, where the electron-donating

⁹⁵ N. G. Luthy, F. W. Bergstrom, and H. S. Mosher, *J. Am. Chem. Soc.* **71**, 1109 (1949).

⁹⁶ D. L. Garmaise and G. Y. Paris, *Chem. Ind. (London)*, 1645 (1967).

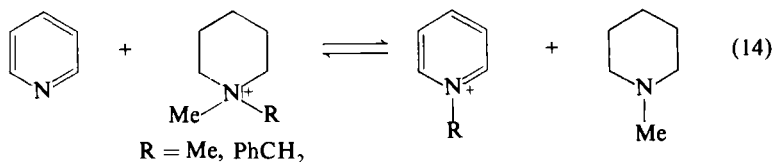
⁹⁷ A. E. Tschitschibabin and R. A. Konowalowa, *Chem. Ber.* **59**, 2055 (1926).

⁹⁸ G. Y. Paris, D. L. Garmaise, and J. Komlossy, *J. Heterocycl. Chem.* **8**, 169 (1971).

⁹⁹ A. K. Sheinkman, A. N. Prilepskaya, A. P. Kucherenko, and S. N. Baranov, *Ukr. Khim. Zh.* **38**, 589 (1972) [*CA* **78**, 15997 (1973)].

amino substituent serves to stabilize the cation. Raising the temperature may bring about isomerization to the more stable material, perhaps by reversing the alkylation process so as to form starting materials. Recombination then provides the more stable compound.

The entire area of the reversible quaternization of heteroaromatic compounds is undeveloped; very little quantitative information is available. The following provides an enticing introduction to the type of information that can result from quantitative work.



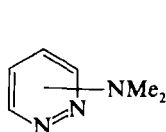
Both pyridine and 1-methylpiperidine can be made to compete for a methyl or a benzyl group by heating a mixture of quaternized and free bases [Eq. (14)] in nitrobenzene or benzyl alcohol. Importantly, the results show that, although the piperidine is more basic than pyridine by a factor of 2.5×10^6 , its affinity (termed carbon basicity) for a methyl group is only 1.4×10^3 , and for a benzyl group only 1.7×10^2 times greater than that of pyridine. The scale representing the equilibrium affinity of nitrogen for carbon appears to be considerably compressed relative to the affinity of nitrogen for hydrogen.¹⁰⁰

The pattern of quaternization of the isomeric dimethylamino-pyridazines (33) and one of their benzologs under conditions that are not conducive to product isomerization, is curious. 3-Dimethylamino-pyridazine has two annular positions and an amino group as possible reactive sites. While the nitrogen atom adjacent to the side chain is hindered, the other is not and is expected on the basis of electronic considerations to undergo alkylation. This is exactly what is observed.¹⁰¹ However, 4-dimethylaminopyridazine gives two products,¹⁰¹ the N-1 to N-2 product ratio being 3:1 when the solvent is acetonitrile.¹³ On the basis of electronic factors derived from the quaternization of amino-pyridines, two different ratios are predicted. Consideration of the reactivities of the pyridines measured in nitrobenzene gives rise to a predicted product ratio of 3.4:1,⁵⁸ in good agreement with the results for the pyridazines. But data for the pyridines reacting in DMSO⁴¹ leads to a poorer prediction of 9:1. Moreover, the benzolog 34 of 4-dimethylaminopyridazine gives an N-methylated product resulting entirely from reaction at N-2.⁹⁴ Even after correcting for a steric effect that decreases

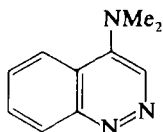
¹⁰⁰ R. E. J. Hutchinson and D. S. Tarbell, *J. Org. Chem.* **34**, 66 (1969).

¹⁰¹ G. B. Barlin and A. C. Young, *J. Chem. Soc., B*, 1675 (1971).

the reactivity of position 1 in the fused ring molecule, electronic factors suggest that **34** ought to give a mixture of quaternized products, contrary to observation.



(33)



(34)



(35)

The report made in connection with a reaction between 1-dimethylaminoisoquinoline and MeI at 20° invites speculation. Quaternization of the annular nitrogen atom results.⁹⁴ This contrasts with reaction at the side chain of both 2-dimethylaminopyridine^{97, 102} and 2-dimethylaminoquinoline⁹⁴ under similar conditions. Perhaps the neighboring peri-hydrogen causes the dimethylamino group to adopt a conformation that minimizes its steric effect and thereby allows the isoquinoline to react at the annular position.

With an aminoazine, both amino and annular nitrogen atoms compete for the alkylating agent. An interesting example is found in 8-aminoquinoline. The product of reaction with MeI, originally reported to be that resulting from reaction at the annular position,¹⁰³ actually is the methylamino material produced by alkylation of the substituent.¹⁰⁴ Here the amino group in a peri position hinders the annular nitrogen atom and so reaction takes place at the side chain.

In the case of 3-amino-2-methylaminopyridine (**35**), the 3-amino group, which is not in conjugation with the annular nitrogen atom, undergoes alkylation.¹⁰⁵ Evidently, the annular position is hindered by the neighboring methylamino group, which is believed to be held in the conformation shown in **35** by internal hydrogen-bonding to the 3-amino group. When the hindrance is decreased, as in 2,3-diaminopyridine, both N-1 and the 3-amino group react. The isomer ratio is highly solvent-dependent, polar aprotic solvents favoring reaction at the annular position more than hydrogen-bonding solvents.¹⁰⁵

With an aminoazine, the size of an alkylating agent may influence the site of reaction. For example, both 4- and 5-aminoquinolines react predominantly at the side chain with a bulky reagent such as benzhydryl

¹⁰² R. Frampton, C. D. Johnson, and A. R. Katritzky, *Ann. Chem.* **749**, 12 (1971).

¹⁰³ F. M. Plakogiannis, E. J. Lien, and J. A. Biles, *J. Med. Chem.* **14**, 430 (1971).

¹⁰⁴ L. W. Deady and N. I. Yusoff, *J. Heterocycl. Chem.* **13**, 125 (1976).

¹⁰⁵ K. Oyama and R. Stewart, *J. Chem. Soc., Perkin Trans. 1*, 673 (1973).

bromide, Ph_2CHBr , whereas they both react at the annular position with a small reagent such as MeI .^{106,107} However, if the annular position becomes more hindered, as in 4-amino-2,3-dimethylquinoline,¹⁰⁷ side-chain reaction is observed, even with small reagents such as MeI . Clearly, there is scope for further investigation of the factors affecting control of products from such molecules with two or more reactive sites.

G. PREDICTING ISOMER RATIOS FOR QUATERNIZED POLYAZINES

The extensive kinetic data available for quaternization of substituted pyridines and derivatives, such as benzologs and diazines, under a uniform set of conditions make possible the calculation of substituent rate factors that are of considerable value in dealing with new substrates. When a heteroaromatic molecule has two or more nucleophilic annular positions that can react, often it is possible to estimate, in some cases very accurately, the ratio of quaternized products using these rate factors.

Table II contains a list of rate factors that express how much a group at a position ortho, meta, or para to an annular nitrogen atom influences

TABLE II
SUBSTITUENT RATE FACTORS FOR THE CALCULATION OF ISOMER RATIOS RESULTING FROM THE QUATERNIZATION OF AZINES WITH METHYL IODIDE IN DMSO^a

Substituent (R)	Position		
	Ortho	Meta	Para
NH_2	0.09	0.59	1.55
Me	-0.42	0.22	0.44 ^c
Et	-0.77	0.18 ^b	0.39 ^c
MeCONH	-2.09	-0.53 ^b	0.39 ^c
PhCH_2	-1.09	—	0.28 ^c
Cl	-2.41	-0.86	-0.40 ^c
Br	-2.41	-0.98 ^b	-0.40 ^c
CO_2Me	-2.08	-0.93 ^b	-0.54 ^c
CN	-2.66	-1.28	-1.16 ^c
MeO	—	0.0	0.64 ^c
$-\text{N}=\text{d}$	-0.60	-1.36	-1.45

^a Logarithmic quantities; hydrogen has the value of 0.

^b Estimated using Hammett $\rho = 2.52$.

^c Estimated using Eq. (12).

^d Annular nitrogen atom.

¹⁰⁶ C. Feller and J. Renault, *Bull. Soc. Chim. Fr.*, 1112 (1973).

¹⁰⁷ J. Berlot and J. Renault, *Bull. Soc. Chim. Fr.*, 2860 (1973).

reactivity. They are based on the reactivity of a substituted pyridine relative to pyridine in a quaternization reaction with MeI in DMSO at room temperature and are logarithmic values of relative rate constants k^R/k^H . For all ortho and most meta substituents, rate factors are derived from experimental results. Other meta substituent values are calculated with the aid of either a Hammett equation using a ρ value of -2.52 and σ values given in reference 63 or the Brønsted equation [Eq. (12)], and known pK_a values.^{46,77} Both approaches give very similar values. Rate factors for para substituents are calculated using the Brønsted equation except in the case of the amino group, where an experimental value is listed. Calculated values generally are slightly different from those published earlier,⁴¹ owing to the inclusion of additional results which modify in a minor way the original correlation equations. However, values for CO_2Me and CN are much less negative than those previously reported because now they are calculated with the aid of a Brønsted rather than a Hammett equation. Rate factors for an annular nitrogen atom present in the ring being quaternized are included in Table II as well.

The effects summarized in Table II show, with few exceptions, that para groups, whether activating or deactivating, exert larger effects than meta substituents. Ortho groups demonstrate both electronic and steric effects and almost without exception are deactivating. Substituents situated ortho to a reactive site are more deactivating than those which are meta or para.

The original work should be consulted for additional rate factors, such as those referring to a fused benzene ring, the replacement of CH by an annular nitrogen atom in an adjacent ring, as well as those for several special, sterically controlled situations. Included are worked examples and a comparison between calculated and predicted isomer ratios.⁴¹

A rate factor approach to chemical reactivity assumes that structural effects influence rate constants in an additive way. While this assumption enjoys considerable success, an obvious failure arises when dealing with steric effects. Naturally, agreement between calculated and observed results is best when the reaction conditions applied to a new substrate are similar to those used on model compounds to obtain rate factors.

Generally, the pyridine rate factors give remarkably useful and accurate predictions about isomer ratios. But substantial disparities between calculated and observed isomer ratios are expected in two cases: (a) alkylating agents bulkier than MeI will reduce the amount of reaction at a sterically hindered nitrogen atom, (b) very reactive alkylating agents, such as alkyl fluorosulfonates,⁷⁶ appear to be much

less discriminating than alkyl halides and sulfates. They tend to give a more even distribution of isomeric products.

An extensive set of substituent rate factors has been derived for the N-methylation of pyridazines. They differ from those reported in Table II in that they represent differences between ortho and meta rate factors, rather than factors for individual positions. They should be consulted when considering pyridazines because the steric effects are likely to be more similar for ortho-substituted pyridazines than for pyridines.¹⁰⁸ In some cases the pyridazine rate factors give calculated isomer ratios that are in better agreement with observed values than those using the data in Table II.

By comparison with the extensive kinetic results available for the quaternization of six-membered rings, especially where substituent effects on reactivity are concerned, few quantitative studies have involved five-membered heterocyclic rings. These are considered next.

VI. Five-Membered Rings

A. HETEROATOM AND BENZO-FUSION EFFECTS ON ACIDITIES

An annular carbon atom of an azole, **36** and **37**, or a benzazole ring, **38–40**, may be replaced by a heteroatom, such as oxygen or sulfur, or by an NMe group. Pronounced variations in the acidities of protonated azoles^{109–119} occur as these heteroatoms are introduced into a ring. The magnitude of the spread in K_a values for the compounds in Table III is a very large factor of 10^{12} . Dissociation constants of the conjugate acids of azoles increase in the order $X = \text{NMe} < \text{S} < \text{O}$, the influence of a heteroatom being greater as it moves closer to the reactive site. Benzo-fusion markedly enhances their acidity except when an ortho quinonoid structure results; in this case, the addition of a fused ring is essentially without effect.

A discussion in terms of resonance and inductive effects of a heteroatom on the acidities of protonated azole rings is available.¹²⁰ A

¹⁰⁸ H. Lund and P. Lunde, *Acta Chem. Scand.* **21**, 1067 (1967).

¹⁰⁹ D. J. Brown and P. B. Ghosh, *J. Chem. Soc.*, 270 (1969).



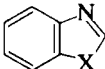
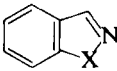
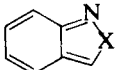
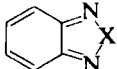
¹¹⁰ R. Phan-Tan-Luu, J. M. Surzur, J. Metzger, J. P. Aune, and C. Dupuy, *Bull. Soc. Chim. Fr.*, 3274 (1967).

¹¹¹ G. Dedichen, *Chem. Ber.* **39**, 1831 (1906).

¹¹² A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. B*, 2365 (1971).

¹¹³ J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 5009 (1968).

TABLE III
HETEROATOM AND BENZO-FUSION EFFECTS ON ACIDITIES OF PROTONATED AZOLES
AND ON RELATIVE RATE CONSTANTS FOR N-METHYLATION

Compound	pK_a			k_{rel}		
	O	S	NMe	O	S	NMe
 (36)	0.8 ¹⁰⁹	2.53 ¹¹⁰	7.33 ¹¹¹	1	15 ⁴⁴ 1	912 ⁴⁴ 61
 (37)	-2.97 ¹¹²	-0.51 ¹¹²	2.06 ¹¹³	1	6.9 ⁴⁴ 1	120 ⁴⁴ 17
 (38)	-0.13 ¹¹⁴	1.2 ¹¹⁵	5.57 ¹¹⁶	1	9.3 ⁴⁴ 1 1 ^a	708 ⁴⁴ 76 76 ⁴⁴
 (39)	-4.7 ¹¹⁷	—	0.42 ¹¹⁸	1	20 ¹²² 1	56 ¹²² 2.8
 (40)	-2.20 ¹¹⁹	-0.05 ⁴²	2.02 ¹¹⁸	1	3.6 ¹²² 1	33 ¹²² 9.2
 (41)					2.8 ^a	1 ¹²³

^a X = Se.

¹¹⁴ P. F. Jackson, K. J. Morgan, and A. M. Turner, *J. Chem. Soc., Perkin Trans. 2*, 1582 (1972).

¹¹⁵ N. N. Zatsepina, Y. L. Kaminskii, and I. F. Tupitsyn, *Org. React. (USSR)* **4**, 117 (1967).

¹¹⁶ J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and J. C. Turner, *J. Chem. Soc., Perkin Trans. 2*, 432 (1973).

¹¹⁷ M. L. Casey, D. S. Kemp, K. G. Paul, and D. D. Cox, *J. Org. Chem.* **38**, 2294 (1973).

¹¹⁸ J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 579 (1965).

¹¹⁹ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, 5360 (1965).

¹²⁰ A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry," p. 146. Methuen, London, 1967.

consideration of the factors giving rise to acidity changes on annelation is presented when results for quaternization are examined. Unfortunately, no systematic study has been made concerning the influence of exocyclic substituents on pK_a values. The data that are available^{89, 121} apply to a limited series of substituted compounds.

B. HETEROATOM EFFECTS ON RATES

For both azole and benzazole rings, introduction of a heteroatom or group X into a ring affects the ease of quaternization.^{44, 122, 123} Rate constants increase in the order $X = O < S < NMe$ (Table III); the magnitude of the effect of a particular heteroatom is dependent on the structure of the substrate. The difference in reactivity between oxa and thia azoles generally is less than that between thia and aza nucleophiles (Table III). However, **39** provides an exception to this pattern; a larger separation is found between the first, rather than the second, pair of heteroatoms considered.

Limited observations are available to indicate the influence of a selenium atom on reactivity. For the two comparisons available, the effect of this atom relative to an NMe group is variable. In the case of **41**,¹²³ the compound containing selenium is more reactive than the aza substrate, but with **38**⁴⁴ (Table III) the reverse order is found. Reasons for the inversion are not apparent.

Molecules having a heteroatom or group in a 1,3 geometry with respect to the reactive nitrogen atom are more reactive than those in which the arrangement is 1,2. However, there is variation in the magnitude of the factor that expresses the increase in rate constant on changing geometry for a given heteroatom. For example, oxazole is 68 times more reactive than isoxazole, **36** vs. **37**,⁴⁴ and benzoxazole quaternizes 26 times faster than 1,2-benzisoxazole, **38** vs. **39**.^{44, 122} Evidently, effects of varying the nature of a heteroatom as well as its position are not strictly additive on rates.

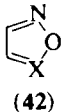

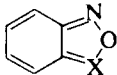
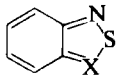
Information is available concerning the magnitude of the decrease in reactivity that results when a second annular nitrogen atom is introduced into an azole ring to replace a carbon atom^{121, 122} (Table IV). Rate factors expressing this retardation range from a low of 63 to a high of 130. These values are larger than those found for single six-membered rings, where an annular nitrogen atom in positions meta and para to a reactive site decreases the reactivity by factors of 23 and 28, respectively.⁶¹

¹²¹ A. Albert, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. III, Chapter 1. Academic Press, New York, 1971.

¹²² M. Davis, L. W. Deady, and E. Homfeld, *Aust. J. Chem.* **27**, 1221 (1974).

¹²³ M. Davis, L. W. Deady, and E. Homfeld, *Aust. J. Chem.* **27**, 1917 (1974).

TABLE IV
RATE-RETARDING FACTORS FOR THE ADDITION OF A
NITROGEN ATOM TO AZOLE AND BENZAZOLE RINGS IN
N-METHYLATION REACTIONS

Compound	$X = \overset{k_{\text{rel}}}{\text{CH/X = N}}$	Reference
 (42)	63	123
	78	122, 123
	130	122, 123
	99	122, 123

In making comparisons to determine an annular nitrogen rate factor for five-membered rings, several assumptions are made because results are not available at a uniform set of conditions. It is assumed that temperature (33°, 54°, and 60°), solvent (DMSO and dimethyl sulfate) and alkylating agent (MeI and dimethyl sulfate) do not have a serious influence on relative rates. The foregoing discussion serves as the basis for the good assumptions. Comparisons are useful and revealing and are not likely to be distorted seriously by the different conditions.

In general, the effects of heteroatoms O, S, N, and Se on rates of quaternization of five-membered rings are so variable that only semi-quantitative predictions about their influence on the reactivities of new molecules can be made.

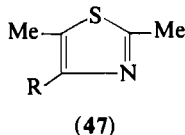
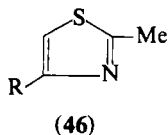
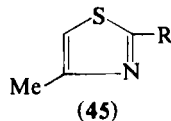
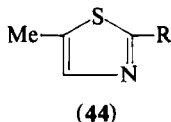
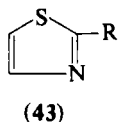
C. STERIC EFFECTS OF ALKYL GROUPS ON RATES

Alkyl groups adjacent to the reactive annular nitrogen atom of a five-membered ring inhibit quaternization, but the magnitude of this steric effect is considerably less than in six-membered rings.⁷⁵ Thus, the rate constant for the methylation of 2-*tert*-butylthiazole by MeI is only 4.2 (acetone)¹²⁴ and 41 (nitrobenzene)⁶⁷ times less than that for the

¹²⁴ M. Azzaro and J. Metzger, *Bull. Soc. Chim. Fr.*, 1575 (1964).

corresponding 2-methyl compound. By comparison, in the pyridine series the retardation factor of 2025 (nitrobenzene) is much larger.⁴ Note that solvents have an important influence on the relative rate constants for the five-membered ring compounds.

As with six-membered rings, kinetic consequences of the steric effects of ortho alkyl groups are related to the E_s parameter [Eq. (13)]. For thiazoles **43** and **44** having a single alkyl group adjacent to the reactive site, the sensitivity factors (δ) for N-methylation are 0.96⁶⁷ and 1.02,⁶⁷ respectively. These are to be compared with the larger quantity, 2.09, for 2-substituted pyridines in the same reaction.⁶⁶ Thiazoles **45** and **46**, which have a methyl and an alkyl group on either side of the nucleophilic center, show a higher sensitivity, 1.57 and 1.63,¹²⁵ respectively, than **43** and **44**. But even these disubstituted compounds are influenced less by steric factors than the monosubstituted pyridines. The reason for the reduced sensitivity is likely to be found in the geometry of five-membered rings where the internal angle at the annular nitrogen atom is less than in six-membered rings, and the exocyclic bond angle involving the alkyl group and the heteroatom is larger.⁶⁷ Both of these geometrical factors serve to direct the alkyl group away from the incoming alkylating agent.



Insight into the geometry an ortho alkyl substituent adopts in order to minimize interaction with an alkylating agent is provided by a consideration of the trisubstituted thiazole **47**. A methyl group adjacent to the alkyl group R prevents R from adopting a conformation that minimizes its interaction with the incoming reagent. Consequently, a nonlinear correlation with E_s values is produced. Ethyl and isopropyl substituents that have one side larger than the other exert a far greater than usual steric rate-retarding effect because there are restrictions to rotation imposed on them by the neighboring group.¹²⁵

¹²⁵ A. Babadjamian, M. Chanon, R. Gallo, and J. Metzger, *J. Am. Chem. Soc.* **95**, 3807 (1973).

D. BENZO-FUSION EFFECT ON RATES

Annulation of a five-membered heterocyclic ring generally leads to rate retardation similar in magnitude to, but different in origin from, that for six-membered rings. However, there are exceptions, and these will be considered first.

A unique example is found in 2,1-benzisoxazole (**40**), which undergoes N-methylation 1.9 times *faster* than isoxazole (**37**).¹²² This is the only known example of rate acceleration resulting from benzo-fusion. Other interesting comparisons involve 2,1,3-benzoxadiazole (benzofurazan, **41**), and 1,2,5-oxadiazole (furazan, **42**),¹²³ and also isothiazole (**37**), and 2,1-benzisothiazole (**40**).¹²² For these two pairs essentially no change in reactivity results when the azole is converted into its benzolog.

All these special cases involve benzologs with an ortho quinonoid structure. But even this pattern is not universal, a deviation being 2-methylindazole (**40**), which quaternizes 2.2 times more slowly than its parent compound 1-methylpyrazole (**37**).¹²² Indeed, except for the molecules just considered and 1,2-benzisothiazole,¹²² benzo-fusion is rate retarding. Thus, 1,2-benzisoxazole (indoxazene, **39**), reacts 3.2 times, and 1-methylindazole (**39**) 7.1 times, more slowly than their parent compounds.¹²² Fusing a benzene ring onto an azole where the heteroatoms are situated 1,3 leads to decreases in rate constants by factors of 5.0, 6.3, and 6.8, respectively, when X of **38** is NMe, S, and O.¹²² These factors are not much smaller than that obtained from a comparison of pyridine and quinoline reactivities.^{61,78,79}

The primary cause of rate retardation generally produced by fusing a benzene ring onto an azole or an azine is different for the two kinds of heterocyclic rings. Unlike the situation for the larger rings, steric effects are unimportant for the azoles. This conclusion follows from two lines of reasoning. First, increasing the size of the alkylating agent does not give rise to retardation of increasing magnitude. Consider as a reference isothiazole and its reactions with alkylating agents of increasing size—methyl, ethyl, and isopropyl iodides.⁴² Steric effects are expected to be unimportant for this single-ring compound; the effect of successively replacing hydrogen by methyl in the methyl iodide is to decrease reactivity by very similar factors. The decreases from methyl to ethyl and from ethyl to isopropyl iodide are factors of 13 and 11 at 60°. With benzothiazole under the same conditions, the reactivity decreases by factors of 14 and 15.⁴² Since no important difference in reactivity exists between the parent molecule and its benzolog, steric factors are unimportant.

Second, annulation produces large electronic effects in five-membered rings, as evidenced by variations in pK_a values. This is a

major difference in behavior from that of six-membered rings and makes necessary the elimination of electronic effects on reactivity before considering the question of steric involvement. This dissection is well accomplished by a Brønsted plot.

E. BRØNSTED CORRELATION

Kinetic data for the N-methylation of 14 azole and benzazole nucleophiles show a linear log-log correlation with the acidities of their conjugate acids (Fig. 1). Variations in rate and equilibrium constants are about 10^5 and 10^{12} respectively, extending the previously reported

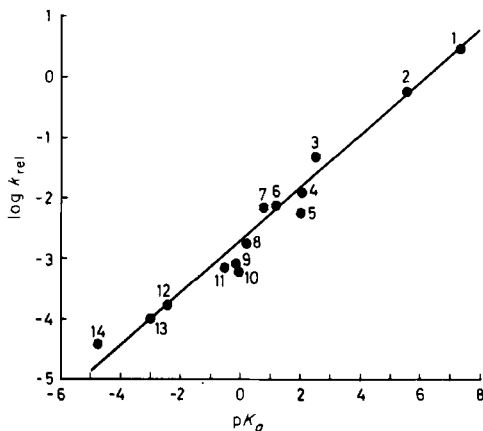


FIG. 1. Brønsted plot for azoles reacting with methylating agents in quaternization reactions. Pyridine is the reference substrate. 1, 1-methylimidazole; 2, 1-methylbenzimidazole; 3, thiazole; 4, 1-methylpyrazole; 5, 2-methylindazole; 6, benzo-thiazole; 7, oxazole; 8, 1-methylindazole; 9, benzoxazole; 10, 2,1-benzisothiazole; 11, isothiazole; 12, 2,1-benzisoxazole; 13, isoxazole; and 14, 1,2-benzisoxazole.

correlation.⁴⁴ Since kinetic results are not available under a uniform set of conditions, it was assumed that relative rate constants obtained under various conditions of solvent, alkylating agent, and temperature provide an accurate measure of changing reactivity. The foregoing discussion provides the basis for this good approximation.

A least-squares treatment of results pertaining to compounds where no steric effect is expected to operate (8 points) as well as one based on all the data in Fig. 1 show very minor differences in the slope (0.004) and intercept (0.070), suggesting that steric factors are unimportant. The line [Eq. (15)], given in Fig. 1 using the result for pyridine as a rate standard, is that based on all the data. There is remarkably little scatter

($r = 0.988$). The two points (5, 10) that deviate the most from this line in a direction expected for a rate-retarding steric effect are due to 2-methyl-indazole and 2,1-benzisothiazole. The former deviates by a factor of 2.7 and the latter by 3.0. However, some points, e.g., that (3) for thiazole, lie off the line in the opposite direction by nearly the same amount. Perhaps the deviations reflect uncertainties in relative rate constants, and also the unknown and possibly large errors in pK_a values, especially the negative ones which generally are based on H_0 acidity function values.

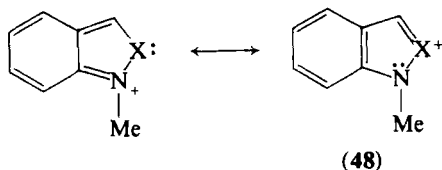
$$\log k_{\text{rel}} = \log k/k^{\text{PYR}} = 0.43 pK_a - 2.75 \quad (15)$$

Clearly, there is a distinct difference between the kinetic results for the benzologs of azines and azoles. The former definitely show a sizable steric effect in N-methylation reactions when the site of quaternization is a peri position, while any effect for the latter is insignificant. Perhaps this simply reflects the smaller internal bond angles for five- over six-membered rings.

Comparison of the Brønsted correlation for 3-substituted pyridines [Eq. (12)] and that for the azoles [Eq. (15)] is most interesting. The slopes are very similar, 0.39 and 0.43, respectively, and represent overlapping values at the uncertainty level of one standard deviation. However, the intercepts, -1.90 and -2.75 , respectively, do not overlap. But consideration of the approximations in the plot for the azoles precludes a definite conclusion about whether the differences are truly significant.

The Brønsted correlation for five-membered rings shows that effects of structure on reactivity and on acidity are related. Variations in rate constants for quaternization and in pK_a values (Table III) are understandable in terms of resonance and inductive effects of the heteroatom X.¹²⁰ The effects on the energy of a transition state leading to quaternized product are similar but smaller than those on the energy of protonated material. The following considers in more detail the influence of benzo-fusion.

Fusing a benzene ring onto an azole to give **38** and **39** allows more extensive delocalization of the electrons of X, both in a free base and in a transition state leading to product. Such delocalization serves to stabilize a ground state. But, in a transition state, stabilization of the developing positive charge on a ring is less effective. The net result is a nucleophile with diminished reactivity.



Benzo-fusion produces special effects in the case of **40**. Again, additional delocalization of the electrons associated with X is possible. However, fusion gives rise to an ortho quinonoid structure with reduced resonance energy. These two factors affect the energy of a nucleophile in opposite ways. Moreover, in the transition state leading to quaternized product, relocation of the electrons from X onto N is especially favorable. The situation is easily illustrated by considering the quaternized product, where the effect is larger than in the transition state. Canonical form **48** with its aromatic benzene ring is an important contributor to the resonance hybrid. These factors serve in the case of the oxa and aza substrates to make them more reactive than their isomeric benzologs **39**. Similarly, compounds with structure **40** are more basic than **39**.

F. PREDICTING RESULTS FOR NEW MOLECULES

1. pK_a Values

The Brønsted correlation given by Eq. (15) is so extensive that it can be used to predict a pK_a value once the rate constant or relative rate constant for N-methylation under the conditions employed to construct this plot is known. This approach is especially valuable for weakly basic heterocyclic compounds, which are protonated only in strongly acidic media. Even for such, it is comparatively easy to determine a rate or relative rate constant for N-methylation. The pK_a values of several molecules so estimated are given in Table V. They are expected to be

TABLE V
ESTIMATED pK_a VALUES BASED ON RATE CONSTANTS FOR
N-METHYLATION AND BRØNSTED EQUATION [Eq. (15)]^a

Compound	$\log k/k^{PYR^a}$	pK_a^b
1,2-Benzisothiazole (39)	-3.21 ¹²²	-1.1
2,1-Benzisothiazole (40)	-3.23 ¹²²	-1.1
Benzoselenazole (38)	-2.13 ⁴⁴	1.4
1,2,5-Oxadiazole (42)	-5.79 ^{122, 123}	-7.1
2,1,3-Benzoxadiazole (41)	-5.82 ^{122, 123}	-7.1
1,2,5-Thiadiazole	-4.97 ^{122, 123}	-5.2
2,1,3-Benzothiadiazole (41)	-5.16 ^{122, 123}	-5.6
2,1,3-Benzoselenadiazole (41)	-3.98 ^{122, 123}	-2.9
2-Methylbenzotriazole (41)	-4.42 ^{122, 123}	-3.9

^a Relative rate constants are based on pyridine as the reference substrate. They have been converted from literature values using 2-cyanopyridine as the reference compound by the addition of the logarithmic quantity -2.66.⁷²

^b At room temperature.

related to those given by H_0 acidity function values because the Brønsted correlation employs dissociation constants determined with the aid of this acidity function. No correction has been made for the small perturbations introduced by using in the calculation relative rate constants obtained under dissimilar reaction conditions.

2. Reactivities

With the aid of the Brønsted equation [Eq. (15)] the reactivities of simple azoles or benzazoles may be predicted from a knowledge of their pK_a values. While this equation was derived for N-methylation reactions using solvents such as DMSO and dimethyl sulfate, it can be applied to estimate nucleophilicity toward other alkylating agents in various solvents provided that (a) the Brønsted β values for the new systems are similar to the old one, and (b) that steric factors are unimportant. The foregoing discussion serves as a guide to indicate when such limitations apply.

Information is not yet available to indicate whether Eq. (15) will apply to polyazoles where there are two or more sites of protonation and of quaternization. It also is not known whether substituted azoles will fit the correlation line. Clearly, a start has been made; additional studies need to be undertaken.

VII. Magnetic Resonance Methods to Identify the Site of Quaternization

One of the most powerful techniques employed to identify the site of quaternization of a molecule with multiple reactive sites is magnetic resonance. Currently, this approach includes the examination of H, ^{13}C , ^{14}N , and ^{15}N nuclei.

Chemical shift variations among *N*-methyl cations have been related to electron densities and, in the case of *N*-methylpyridinium ions, to Hammett substituent constants.¹²⁶ Upfield shifts of H,¹²⁶⁻¹²⁸ ^{13}C ,¹²⁶ and ^{14}N nuclei¹²⁶ are observed when electron-donating groups increase the electron density at the quaternized site. In instances where shift differences are large, application of these correlations to molecules giving isomeric products will enable conclusive identification of product structures to be made.

When employing a magnetic resonance method to identify quaternized products, care has to be exercised in the selection of a solvent. For proton spectra, DMSO- d_6 or even DMSO is a good choice, both because reactants and quaternized products are likely to be soluble and

¹²⁶ F. W. Wehrli, W. Giger, and W. Simon, *Helv. Chim. Acta* **54**, 229 (1971).

¹²⁷ L. W. Deady and G. D. Willet, *Organ. Magnet Reson.* **6**, 53 (1974).

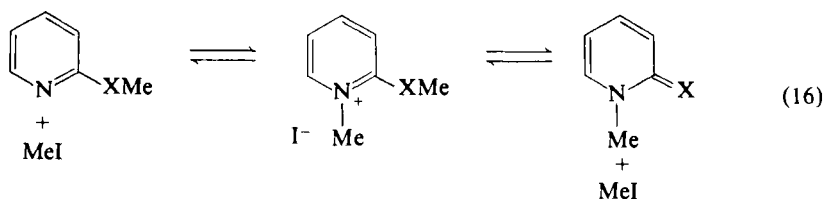
¹²⁸ M. Davis, L. W. Deady, and E. Homfeld, *J. Heterocycl. Chem.* **11**, 1011 (1974).

because *N*-alkyl and solvent signals are unlikely to overlap; the ^{13}CH side band at low field ($\delta = 3.77$) may serve as a useful chemical shift standard in the undeuterated solvent. However, for molecules of low reactivity, reaction between DMSO and the alkylating agent may take place.⁴⁵ In such cases sulfolane is a suitable substitute, although signal overlap becomes more of a problem.

No single approach will serve in all cases; some examples should be consulted in order to become familiar with successful applications which can involve a consideration of both chemical shifts and coupling constants.^{22, 108, 129–131} Various compilations of ^1H ,^{126–128, 132–134} ^{13}C ,^{126, 135} and ^{15}N ^{126, 136} magnetic resonance data are available.

VIII. Dealkylation

Quaternization of molecules containing alkoxy and thioalkoxy substituents can be complicated by dealkylation of the substituent. Such side reactions are especially facile in molecules that give rise to a carbonyl or thiocarbonyl group following dealkylation. The reaction between a 2-substituted pyridine and MeI is illustrative [Eq. (16)]. This sequence is reversible and can be used to advantage to compare the enthalpies of unquaternized starting material and product.^{137, 138}



¹²⁹ P. Dea, G. R. Revankar, R. L. Tolman, R. K. Robins, and M. P. Schweizer, *J. Org. Chem.* **39**, 3226 (1974).

¹³⁰ T. C. Thurber, R. J. Pugmire, and L. B. Townsend, *J. Heterocycl. Chem.* **11**, 645 (1974).

¹³¹ M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.* **97**, 4627, 4636 (1975).

¹³² A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry." Academic Press, New York, 1971.

¹³³ T. J. Batterham, "NMR Spectra of Simple Heterocycles." Wiley (Interscience), New York, 1973.

¹³⁴ L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed. Pergamon, Oxford, 1969.

¹³⁵ J. B. Stothers, "Carbon-13 NMR Spectroscopy." Academic Press, New York, 1972.

¹³⁶ M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron* **28**, 637 (1972).

¹³⁷ P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron* **28**, 5507 (1972).

¹³⁸ P. Beak, D. S. Mueller, and J. Lee, *J. Am. Chem. Soc.* **96**, 3867 (1974).

A number of methods are available to dequaternize heterocyclic and related compounds. Dealkylation methods may be desired for various reasons which include (a) removing a protecting group in a multistep synthesis and (b) activating a molecule for nucleophilic substitution by quaternization and then removing the group after substitution.

Recent effective, nonreducing, dealkylating reagents include hot DMF,¹³⁹ lithium *n*-thiopropoxide in cold HMPA,^{140,141} cuprous thiophenoxide in refluxing pyridine¹⁴² as well as nucleophiles, such as diazabicyclooctane in hot DMF¹⁴³ and triphenylphosphine in hot acetonitrile.¹⁴⁴ An especially mild method which works for quaternized pyridines having electron-withdrawing groups^{145,146} and for quaternized pyrimidines¹⁴⁷ simply involves adding the compound to liquid ammonia and then removing the solvent. For additional approaches, consult references in the articles just cited.

A real challenge for dequaternization is the methyl group buried in 1-methyl-2,6-di-*tert*-butylpyridinium ion. Heating this ion with powdered KI to 300° failed to induce decomposition.¹⁹

IX. Obtaining Relative Rate Constants for Quaternization Reactions by Competition Methods

Competition experiments provide a quick and easy way to compare the reactivities of a pair of nucleophiles toward an alkylating agent. Elaborate constant-temperature baths are not required. Nuclear magnetic resonance (NMR) is particularly well suited to provide measures of concentrations of reactants and products in such experiments.

Because competition experiments are so convenient, several approaches will be outlined. Of course, it is possible to compare nucleophilic reactivities by determining a rate constant for one nucleophile at a time, and then to compare results for several nucleophiles. This more time-consuming method, which requires better quality constant-temperature equipment, will not be considered. Many source books are available to indicate how to obtain such rate constants.

¹³⁹ D. Aumann and L. W. Deady, *Chem. Commun.*, 32 (1973).

¹⁴⁰ J. P. Kutney, G. B. Fuller, R. Greenhouse, and I. Itoh, *Synth. Commun.* **4**, 183 (1974).

¹⁴¹ R. O. Hutchins and F. J. Dux, *J. Org. Chem.* **38**, 1961 (1973).

¹⁴² G. H. Posner and J. S. Ting, *Synth. Commun.* **4**, 355 (1974).

¹⁴³ T. L. Ho, *Synthesis*, 702 (1972).

¹⁴⁴ J. P. Kutney and R. Greenhouse, *Synth. Commun.* **5**, 119 (1975).

¹⁴⁵ J. A. Zoltewicz, T. M. Oestreich, J. K. O'Halloran, and L. S. Helmick, *J. Org. Chem.* **38**, 1949 (1973).

¹⁴⁶ J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.* **41**, 1303 (1976).

¹⁴⁷ E. A. Oostveen, H. C. van der Plas, and H. Jonegejan, *Rec. Trav. Chem. Pays-Bas* **93**, 114 (1974).

To decide which approach to pursue, a good first experiment involves taking equal concentrations of all reactants and allowing the reactions to proceed until all the alkylating agent is consumed before analysis. Optimum conditions may then be selected. In general, when the rate-constant ratio is 10 or larger and the initial concentrations of the two nucleophiles are equal, errors in determining concentrations become prohibitively large. This situation may be improved by letting the initial concentration ratio be equal to the rate-constant ratio, the less reactive nucleophile being present in larger amounts. In this way very similar quantities of products are formed and the concentrations of products can be determined accurately. But there may be a practical limit to this approach if a substrate has low solubility. This problem may be circumvented by techniques, such as Fourier transform NMR, which allow dilute solutions to be analyzed. The concentrations of all reactants may be reduced greatly when this new technique is applied.

Alternatively, another nucleophile may be selected for the competition study in order to have a pair of substrates with similar reactivities. The selection of substrates for comparison requires some care. When using NMR as a method of analysis, nonoverlapping signals are required for convenient integration. If the alkylating agent is MeI, then it is convenient to examine the singlet *N*-methyl peak of the product. Extensive tables of *N*-methyl group chemical shifts are available to help select substrates for competition runs.¹²⁶⁻¹²⁸ A few trials may be necessary in order to select a good reference substrate. For an extensive study, a class of compounds giving resonance peaks different from those of the comparison substrates and/or products should be selected first. The reactivity of the reference substance can then be modified by introducing substituents. In the following, the alkylating agent is designated MeX, but it is to be understood that the methods are not limited to methylation reactions.

Several approaches are available to determine a rate-constant ratio for *intermolecular* reactions. (1) The most general method is much like that used to determine rate constants with a single nucleophile. However, by employing a pair of nucleophiles, the concentration of the alkylating agent need not be known. Equation (17) is used to calculate a rate-constant ratio. Both small and large conversions of reactant to product are conveniently handled by the equation; it is written in a form to be used when a reactant concentration, [Het], is determined as well as when a product concentration, [MeHet], is obtained. The zero subscript designates an initial concentration.

$$\frac{k_1}{k_2} = \frac{\log\{([\text{Het}_1]/[\text{Het}_1]_0) - ([\text{MeHet}_1]/[\text{Het}_1]_0)\}}{\log\{([\text{Het}_2]/[\text{Het}_2]_0) - ([\text{MeHet}_2]/[\text{Het}_2]_0)\}} \quad (17)$$

Other, more limited approaches may also be employed. (2) When side reactions are unimportant and the products are stable, a pair of nucleophiles may be allowed to compete for a deficiency of alkylating agent. The relative amount of alkylated products, R , is determined when all the alkylating agent is consumed; R is $[\text{MeHet}_1]/[\text{MeHet}_2]$, the molar ratio of methylated products. The rate-constant ratio then is calculated with the aid of Eq. (18).^{62,148} This special approach allows a rate-constant ratio to be calculated using a product ratio instead of concentrations of individual products. It is conveniently applied when, say, it is hard to find an internal reference standard in NMR methods of analysis, thereby making the determination of concentrations difficult.

$$\frac{k_1}{k_2} = \frac{\log \{1 - ([\text{MeX}]_0/[\text{Het}_1]_0) \cdot R/(1 + R)\}}{\log \{1 - ([\text{MeX}]_0/[\text{Het}_2]_0) \cdot 1/(1 + R)\}} \quad (18)$$

If the substrates are not very reactive or if the alkylating agent reacts with the solvent, another approach is employed. (3) In the initial-rate method an excess of alkylating agent may be utilized. This has the additional advantage of increasing the rate of conversion to product. Normally in the initial-rate method, 1–2% of a product is allowed to form before the product ratio, R , is determined. However, NMR analysis may be difficult, and so conversions as large as 25% may be carried out in order to increase the intensity of the resonance signal; the error introduced by these more extensive conversions is only slightly larger than the error in typical proton NMR measurements, e.g., ~7% when the rate constant ratio is 2 and ~11% when the ratio is 4. Moreover, this error can be reduced by measuring the product ratio at various times early in the reaction, extrapolating a plot of ratio versus time back to time zero, and then calculating the rate-constant ratio from Eq. (19). It is clear from Eq. (19) that the alkylating agent concentration does not appear, and so any reaction between this agent and the solvent does not influence the accuracy of the rate-constant ratio, unlike Eq. (18). For best results, product concentrations or ratios should be determined directly rather than by calculating a difference based on initial and subsequent quantities of starting material. This method may be employed for a pair of nucleophiles of similar reactivities or for two with a large difference, provided that the less reactive substrate is present in larger concentration so that approximately equal amounts of products are formed.

$$(k_1/k_2) \times [\text{Het}_1]_0/[\text{Het}_2]_0 \approx [\text{MeHet}_1]/[\text{MeHet}_2] = R \quad (19)$$

¹⁴⁸ C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).

A special case (4) arises for *intramolecular* competition reactions. The product ratio gives the rate-constant ratio directly [Eq. (20)]. Either a deficiency or an excess of alkylating agent may be present; the reaction mixture may be analyzed at various stages of conversion to products.

$$k_1/k_2 = [\text{MeN}_1]/[\text{MeN}_2] = R \quad (20)$$

PART II. ORGANIZATION OF QUATERNIZATION DATA ACCORDING TO RING TYPE

The following information is organized according to ring type and contains cross references to relevant sections of Part I together with additional references and pertinent material not included in the general narrative of Part I.

X. Six-Membered Rings and Benzologs

A. ONE HETEROATOM

Pyridines.¹⁴⁹ References are made to quaternization reactions of pyridines in nearly all sections of Part I. A very extensive series of papers dealing with pyridinium ions and fused ring pyridinium ions, their preparations and properties is available.¹⁵⁰

Quinolines (see Sections V,C,2 and F). A number of substituted quinolinium ions have been prepared using oxonium salts.¹⁵¹ Rate constants at several temperatures are available for the intramolecular cyclization of 8-(2'-chloroethylthio)quinoline.¹⁵²

Information on *isoquinoline* is found in Sections V,C,2 and F, on an *acridine*^{153,154} and a *benzo[h]quinoline* in Section II and on *phenanthridines* in Section V,C,2.

¹⁴⁹ O. R. Rodig, in "Pyridine and Its Derivatives" (R. A. Abramovitch, ed.), Suppl., Part 1, Chapter III. Wiley (Interscience), New York, 1974.

¹⁵⁰ G. A. Ulsaker and K. Undheim, *Acta Chem. Scand., Ser. B* **29**, 853 (1975) and earlier references cited therein.

¹⁵¹ A. Dondoni, *Boll. Sci. Fac. Chim. Ind. Bologna* **25**, 111 (1967) [*CA* **68**, 1144035 (1968)].

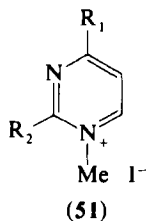
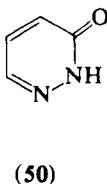
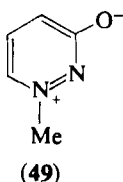
¹⁵² G. Buchmann and R. Schmuck, *J. Prakt. Chem.* **25**, 279 (1964).

¹⁵³ I. A. Selby, in "Acridines" (R. M. Acheson, ed.), 2nd ed., Chapter V. Wiley (Interscience), New York, 1973.

¹⁵⁴ A. Albert, "The Acridines," 2nd ed., Chapter 15. Arnold, London, 1966.

B. TWO HETEROATOMS

Pyridazines (see Sections II, IV, V,C,1, and V,D–G). Product ratios for the quaternization of 3- and 4-methylpyridazines and their NMR spectra have been reported.¹⁵⁵ Betaine (49) is prepared by heating 3(2*H*)-pyridazinone (50) with methyl tosylate to 130° in kerosene followed by deprotonation of the resultant cation with an exchange resin. Interestingly, both MeI and methyl sulfate react under alkaline conditions with the pyridazinone at the other annular nitrogen atom.¹⁵⁶



Pyrimidines¹⁵⁷ (see Sections I, II, and V,D). In the previous review,¹ a number of incorrect deductions were made from preparative work about the effect of an amino substituent on reactivity. The positional order $5 > 2 > 4$ was arrived at for the activating effect of this group. Consideration of kinetic results for 2-, 3-, and 4-aminopyridines shows that the order of the activating effect of an amino group is para > meta > ortho and the reactivity order for aminopyrimidines is therefore predicted to be 4 (with reaction occurring at N-1) > 5 > 2. Furthermore, kinetic data (Table II) show an amino substituent to be more activating than a methyl or chloro group in the same position, in contrast to predictions made from preparative work.

Quaternary salts having structure 51 have been isolated; R_1 and R_2 are amino, alkoxy, and thioalkoxy substituents. Except in the case of 2-amino products, dealkylation to give a 2-pyrimidone takes place readily under alkaline conditions.¹⁵⁸

Pyrazines (see Sections II, V,B,2, and D). Both 2-amino- and 2-methylpyrazine react with MeI to give isomers. The observed isomer ratios are very close to those predicted by considering relative reactivities of the appropriately 2- and 3-substituted pyridines.⁶²

The observation¹⁵⁹ that 2-aminopyrazine undergoes quaternization

¹⁵⁵ M. S. Bale, A. B. Simmonds, and W. F. Frager, *J. Chem. Soc. B*, 867 (1966).

¹⁵⁶ N. Dennis, A. R. Katritzky, and M. Ramaiah, *J. Chem. Soc., Perkin Trans. 1*, 1506 (1975).

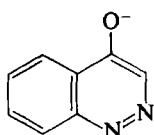
¹⁵⁷ D. J. Brown, "The Pyrimidines," Suppl. I, Chapter X, Wiley (Interscience), New York, 1970.

¹⁵⁸ T. Ueda and H. Ohtsuka, *Chem. Pharm. Bull (Tokyo)* **21**, 1451 (1973).

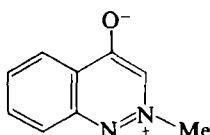
¹⁵⁹ G. W. H. Cheeseman, *J. Chem. Soc.*, 242 (1960).

largely at N-4 and protonation at N-1 is explicable in terms of the properties of aminopyridine model compounds. 2-Aminopyridine is more basic than the 3-isomer but, because of a steric effect, is less reactive to quaternization.⁷²

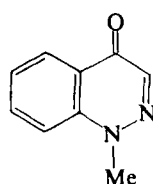
*Cinnolines*¹⁶⁰ (see Sections V,B,3, D, and E). The greater reactivity of N-2 of cinnoline (**26**)^{61,91,161} can be reduced by introducing an alkyl group at the 3-position.¹⁶² More product resulting from quaternization of N-1 then results.¹⁶³ A preference for alkylation at N-2 of the anion of 4(1*H*)-cinnolone (**52**) is also noted; betaine **53** is favored 3:1 over cinnolone **54**. Alkylation at oxygen is not observed. Again, the presence of a substituent at position 3 forces more reaction to occur at N-1.⁶⁵



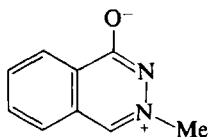
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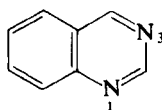
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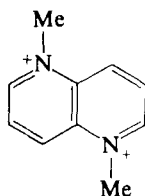
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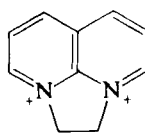
(55)



(56)



(57)



(58)

*Phthalazines*¹⁶⁰ (see Sections V,D and E). The preparation of betaine **55** is similar to that of **49**.¹⁵⁶

Quinazoline. As with cinnoline, quinazoline (**56**) preferentially undergoes quaternization at the "isoquinoline" nitrogen atom. The N-

¹⁶⁰ N. R. Patel, in "Condensed Pyridazines Including Cinnolines and Phthalazines" (R. N. Castle, ed.), Chapter II. Wiley (Interscience), New York, 1973.

¹⁶¹ D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 283 (1964).

¹⁶² D. E. Ames, R. F. Chapman, and D. Waite, *J. Chem. Soc. C*, 470 (1966).

¹⁶³ M. H. Palmer and P. S. McIntyre, *Tetrahedron* **27**, 2913 (1967).

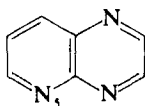
3 : N-1 isomer ratio varies from 5 : 1¹⁶⁴ (MeI, neat or in ethanol) to 8 : 1¹⁶¹ (MeI in DMSO).

Naphthyridines (see Sections II and V,D). Diquaternary salts of 1,5-^{25, 165} (**57**), 1,6-,²⁵ 1,7-,²⁵ 1,8-²⁵ (**8**), and 2,7-²⁵ naphthyridines have been prepared by the action of methyl sulfate¹⁶⁵ or methyl fluorosulfonate.²⁵ 1,8-Naphthyridine does not react with methyl sulfate to give a diquaternary salt but does so with 1,2-dibromoethane to give **58**,¹⁶⁶ an interesting observation.

1,10-Phenanthroline (see Section V,C,2).

C. THREE HETEROATOMS

Triazanaphthalene. Quaternization of 1,4,5-triazanaphthalene (**59**) with MeI in DMSO gives a single product resulting from reaction at N-5, a result expected from a consideration of the reactivities of pyridine and pyrazine.⁴¹



(59)

XI. Five-Membered Rings and Benzologs

A. TWO HETEROATOMS

*Pyrazoles*¹⁶⁷ and *Imidazoles* (see Sections VI,A, B, D, and E). Effects of *N*-aryl substituents on rate constants for the quaternization of pyrazoles (**60**)¹⁶⁸ and imidazoles (**61**)¹⁶⁹ are correlated using a Hammett equation. It is not possible to decide whether the greater sensitivity (ρ

¹⁶⁴ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **48**, 3449 (1970).

¹⁶⁵ L. A. Summers and L. E. Pickesen, *Chem. Commun.*, 1183 (1967).

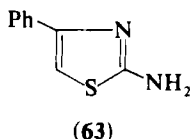
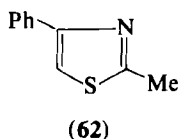
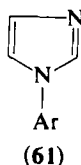
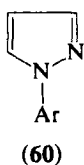
¹⁶⁶ J. E. Dickesen, I. F. Eckhard, R. Fielden, and L. A. Summers, *J. Chem. Soc., Perkin Trans. 1*, 2885 (1973).

¹⁶⁷ R. Fusco, in "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings" (R. H. Wiley, ed.), Chapter 4, Wiley (Interscience), New York, 1967.

¹⁶⁸ L. W. Deady, R. G. McLoughlin, and M. R. Grimmett, *Aust. J. Chem.* **28**, 1861 (1975).

¹⁶⁹ A. F. Pozharskii, L. M. Sitkina, A. M. Simonov, and T. N. Chegolya, *Chem. Heterocycl. Compds.* **6**, 194 (1970).

value) of the pyrazoles (-1.10) over the imidazoles (-0.45) is primarily due to the presence of the quaternizing center adjacent to the site of attachment of the aryl group or to steric effects that cause the aryl group to rotate out of the plane of the heterocyclic ring in the transition state.



Benzimidazoles (see Sections VI,A, B, D, and E).

Thiazoles (Sections VI,A–E). Rate constants are available for the N-methylation of several 4-arylthiazoles.⁴³ Contrary to expectation (Table II), methylthiazole (62) is reported to be more reactive than aminothiazole (63).⁴³

A polymer having a quaternized annular nitrogen atom is produced in a reaction between 4-vinylthiazole and MeI¹⁷⁰

Sections VI,A, B, D, and E give information about *indazoles*, *oxazole*, *benzoxazole*, *isoxazole*, *benzisoxazoles*, *isothiazole*, *benziso-thiazoles*, and *benzothiazole*. In addition, Sections II and VI,F,1 refer to quaternization reactions of *isoxazole* and *benziso-thiazoles*, respectively.

Benzoselenazole (see Sections VI,A, B, and F,1).

B. THREE HETEROATOMS

Triazoles (see Section II). 1-Substituted 1,2,3-triazoles (64) readily undergo quaternization at N-3.^{171, 172} Quantitative data are not available, but the fact that methyl fluorosulfonate is required to quaternize isomeric structures 65 suggests that they are much less reactive than 64.¹⁷³ Since the two isomers show large differences in basicity,¹⁷⁴ it seems likely that the large separation in reactivity is not primarily due to

¹⁷⁰ C. L. Schilling, and J. E. Mulvaney, *Macromolecules* **1**, 452 (1968).

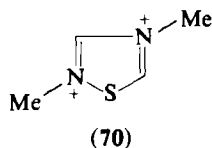
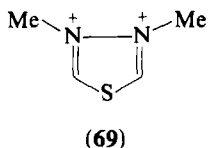
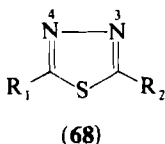
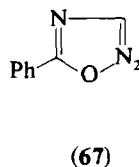
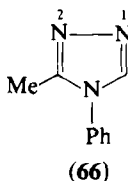
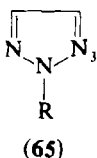
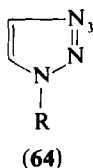
¹⁷¹ M. Begtrup and P. A. Kristensen, *Acta Chem. Scand.* **23**, 2733 (1969).

¹⁷² M. Begtrup, *Acta Chem. Scand.* **25**, 249 (1971).

¹⁷³ M. Begtrup and K. V. Poulsen, *Acta Chem. Scand.* **25**, 2087 (1971).

¹⁷⁴ C. Pedersen, *Acta Chem. Scand.* **13**, 888 (1959).

a steric effect. The analogy of N-3 in **64** and **65** being like the annular nitrogen atom in imidazole and pyrazole,^{44,174} respectively, serves as a useful guide to reactivity.



The disubstituted 4*H*-1,2,4-triazole **66** reacts with MeI both at N-1 and N-2.¹⁷⁵ Given the small steric effects of substituents adjacent to the reactive site in azoles,^{67,125} the lack of discrimination between the two sites is not surprising.

Oxadiazoles (see Sections VI,D and F,1). Quaternization of 5-phenyl-1,2,4-oxadiazole (**67**) occurs at N-2, presumably for steric reasons.¹²³

Thiadiazoles (see Section VI,F,1). Disubstituted thiadiazoles (**68**) react with MeI at N-3 and/or N-4; steric and electronic factors have been implicated. Thus, when R₁ is Me and R₂ is NH₂, 76% reaction occurs at N-3, while when R₁ is Me and R₂ is MeCONH, only 37% quaternization takes place at N-3.³³ Similarly, for compounds where R₁ is MeS, predominant reaction takes place at N-3 when R₂ is NH₂ but not when R₂ is larger, the morpholino substrate favoring alkylation at N-4.¹⁷⁶ The situation becomes complicated when R₁ is MeS and R₂ is Me₂N. In this case, the N-3 product is favored about 2 : 1 over the N-4 isomer when one equivalent of MeI is employed. However, the ratio changes to 1 : 5.6 when an excess of MeI is used.¹⁷⁶

Diquaternized thiadiazoles **69** and **70** have been synthesized.²⁴

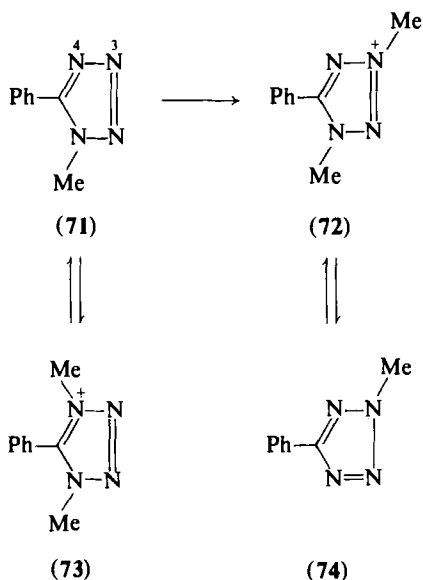
Information pertaining to *benzotriazole* is found in Sections VI,A,B and F,1, *benzoxadiazole* in Sections VI,D and F,1, *benzothiadiazole* in Section VI,F,1, and *benzoselenadiazole* in Sections VI,A,B and F,1.

¹⁷⁵ F. S. Babichev and V. A. Kuvtunenkov, *Ukr. Khim. Zh.* **41**, 252 (1975); [*Ca* **82**, 170807 (1975)].

¹⁷⁶ M. B. Kolesova, L. I. Maksimova, and A. V. El'tsov, *Russ. J. Org. Chem.* **9**, 2631 (1973).

C. FOUR HETEROATOMS

Tetrazoles.¹⁷⁷ The product distribution resulting from the reaction of the tetrazole **71** with MeI is highly dependent on temperature and time. The tetrazole quaternizes at both N-3 and N-4 to give **72** and **73**, respectively. However, the N-4 product reverts to starting material while the N-3 product yields a new tetrazole, **74**, isomeric with the starting material. The N-3 alkylated product undergoes dequaternization much more readily than the N-4 cation. The new tetrazole, unlike the original one, quaternizes only at a single nitrogen atom, giving **72**. Since the most stable material is **74**, prolonged heating of **71** with MeI at 130° quantitatively converts **71** into **74** through the quaternary compounds.¹⁷⁸ Obviously, it is difficult to obtain information about the relative nucleophilic properties of the several nitrogen atoms in these tetrazoles. However, some fascinating aspects of rates and equilibria are revealed by this investigation.



1,2,3,4-Thiatriazoles (see Section II). 5-Substituted 1,2,3,4-thiatriazoles undergo quaternization at N-3 [Eq. (5)]. The study using ¹H, ¹⁵N, and ¹³C NMR to prove the structure of the product serves as a model not only for this ring system, but for others as well.²²

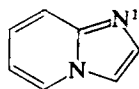
¹⁷⁷ F. R. Benson, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 8, Chapter 1. Wiley, New York, 1967.

¹⁷⁸ T. Isida, S. Kozima, K. Nabika, and K. Sisdo, *J. Org. Chem.* **36**, 3807 (1971).

XII. Fused Heterocyclic Rings

A. TWO HETEROATOMS

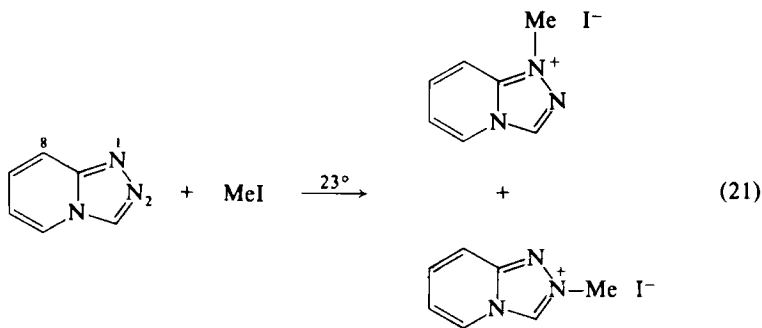
*Imidazo[1,2-*a*]pyridine (75)*, a 10 π -electron molecule, is methylated at N-1, in agreement with electron density calculations.¹⁷⁹



(75)

B. THREE HETEROATOMS

s-Triazolo[4,3-*a*]pyridine gives with MeI a 2:1 mixture of products resulting from reaction at N-1 and N-2, respectively [Eq. (21)]. Heating to 225° converts the minor product into the major one. A steric effect operates in this system: the 8-methyl compound undergoes methylation mainly at N-2.¹⁸⁰



*Imidazo[1,5-*a*]pyrimidine (76)* reacts with MeI at N-2.¹⁸¹

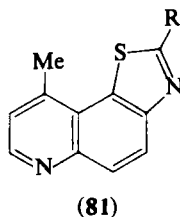
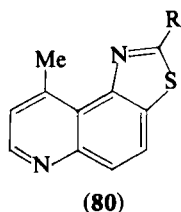
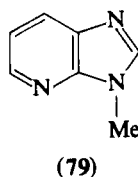
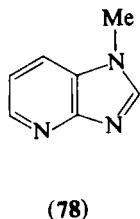
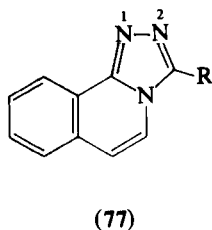
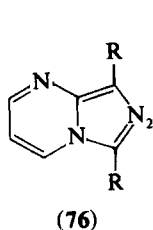
s-Triazolo[3,4-*a*]isoquinolines (77) undergo quaternization with MeI at N-1 and/or N-2, depending on the identity of substituent R.¹⁸²

¹⁷⁹ W. W. Paudler and H. L. Blewitt, *J. Org. Chem.* **31**, 1295 (1966).

¹⁸⁰ W. W. Paudler and R. J. Brumbaugh, *J. Heterocycl. Chem.* **5**, 29 (1968).

¹⁸¹ P. Guerret, R. Jacquier, and G. Maury, *Bull. Soc. Chim. Fr.*, 2481 (1972).

¹⁸² H. Reimlinger, J. J. M. Vandewalle, R. Merengi, and W. R. F. Lingier, *Chem. Ber.* **108**, 3762 (1975).



Imidazo[4,5-b]pyridines. Methyl chloride reacts with **78** at the nitrogen atom of the pyridine ring, but with **79** at the unsubstituted imidazole nitrogen atom.¹⁸³ The former result is surprising because it does not fit a prediction based on a consideration of the relative reactivities of pyridine and 1-methylimidazole.⁴⁴

Thiazoloquinolines. Compounds **80** and **81** react with MeI at the pyridine nitrogen atom.¹⁸⁴

C. FOUR HETEROATOMS

Purines. Extensive information is available about the site of alkylation of purines.^{1, 185-187} Many of these reactions, although taking place at an

¹⁸³ T. N. Pliev, R. M. Bystrova, and Yu. M. Yutilov, *Chem. Heterocycl. Compds.* **9**, 1526 (1973).

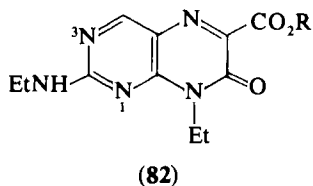
¹⁸⁴ E. Barni, G. DiModica, A. Gasco, and F. D. Monache, *Tetrahedron Lett.*, 3867 (1966).

¹⁸⁵ J. H. Lister, in "Fused Pyrimidines" (D. J. Brown, ed.), Part II: Purines. Wiley (Interscience), New York, 1971.

¹⁸⁶ R. K. Robins, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 8, Chapter 3. Wiley, New York, 1967.

¹⁸⁷ M. Rasmussen and J. H.-S. Chan, *Aust. J. Chem.* **28**, 1031 (1975).

annular nitrogen atom, do not give rise to cationic products, owing to subsequent loss of proton from a ring nitrogen atom. The site of reaction with MeI of all the possible mono-, di-, and trimethylthio substituted purines is known. A combination of steric and electronic factors determines which of the two rings reacts.¹⁸⁸



Pteridines have been converted into nucleoside derivatives by attaching a sugar group to an annular nitrogen atom. The products are not quaternary salts.¹⁸⁹ Compound **82** reacts with methyl tosylate at N-3 rather than at N-1 because it is less hindered.¹⁹⁰

ACKNOWLEDGMENT

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¹⁸⁸ U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. Chem. Soc., Perkin Trans. 1*, 793 (1973).

¹⁸⁹ M. Ott and W. Pfeleiderer, *Chem. Ber.* **107**, 339 (1974) and earlier references cited therein.

¹⁹⁰ W. Pfeleiderer and R. Mengel, in "Chemistry and Biology of Pteridines," Proc. 4th Int. Symp. (K. Iwai, ed.), pp. 43-55. Int. Acad. Print Co., Tokyo, 1969 [*CA* **75**, 129764 (1971)].

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Isatogens and Indolones

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AND MALCOLM HOOPER

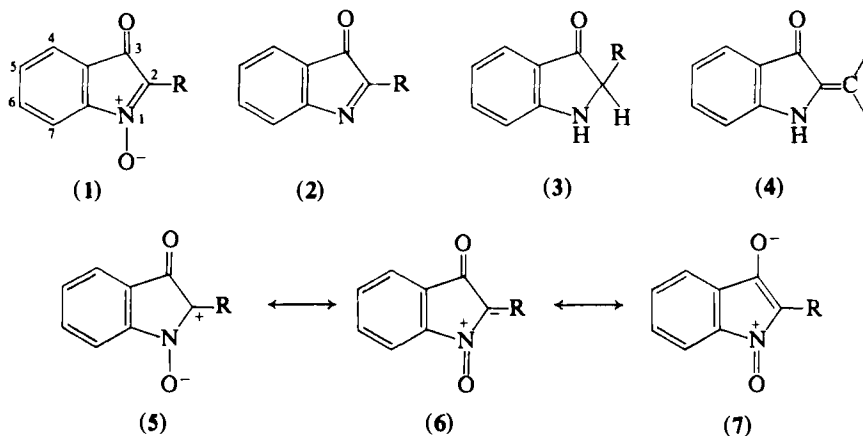
School of Pharmacy, Sunderland Polytechnic, Sunderland, England

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I. Introduction

Isatogens (1) and indolones (2) are brightly colored solids that do not occur naturally. Isatogens (1) are more comprehensively named as 3-oxo-3*H*-indole 1-oxides, or as the 1-oxides of indolones (2), 3-oxo-3*H*-indoles, or 3*H*-indol-3-ones. Both series of compounds are numbered in accordance with IUPAC rules. Isatogens were first reported in 1881^{1,2} and the first indolone in 1912.³ Isatogens (1), indolones (2) and indoxyls (3) form an interrelated redox system. Indolones in which there is a methylene or methine substituent in the 2-position tautomerize to the preferred 2-methylene-3*H*-indol-3-one (indogenide) structures (4).⁴ Only passing reference will be made to 3 and 4 in this review.



Isatogens, last reviewed in 1954,⁵ are usually represented as 1, but they are more fully described by the additional canonical structures 5–7. The addition of nucleophiles and some dipolarophiles is indicated by 5

¹ A. Baeyer, *Ber. Deut. Chem. Ges.* **14**, 1741 (1881).

² A. Baeyer, *Ber. Deut. Chem. Ges.* **15**, 50 (1882).

³ L. Kalb and J. Bayer, *Ber. Deut. Chem. Ges.* **45**, 2150 (1912).

⁴ J. D. Loudon and G. Tennant, *Q. Rev., Chem. Soc.* **18**, 389 (1964).

⁵ W. C. Sumpter and F. M. Miller, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. VIII, Chapter 5. Interscience, New York, 1954.

whereas the back-polarization represented in **6** is well known in cyclic nitrones and aromatic *N*-oxides.⁶ The parent isatogen (**1**: R = H) has not been unequivocally identified, and only recently have 2-alkylisatogens (**1**: R = alkyl) been prepared. The parent indolone (**2**: R = H) is also unknown; until recently the only well authenticated indolone was **2** (R = Ph). The indolones (**2**: R = OMe, Cl) are usually regarded as derivatives of isatin (see Sections IV,A,3 and V,A). Indolones have not previously been reviewed.

II. Synthesis of Isatogens

Isatogens may be prepared by two general methods involving either an intramolecular cyclization or oxidation of a 2-substituted indole derivative.

A. INTRAMOLECULAR CYCLIZATIONS

Until very recently, most syntheses of isatogens were in this category and characteristically involved ortho-substituted nitrobenzenes.

1. From 2-Nitrophenylacetylenes

The cyclization of 2-nitrophenylacetylene derivatives (**8**) provides a versatile route to isatogens bearing mainly aryl,^{5,7} arylcarbamyl,⁸ or alkoxycarbonyl^{11,2,9,10} substituents in the 2-position. Four different reagents have been used to effect this type of cyclization.

a. *Sulfuric Acid*. The synthesis of the first isatogens^{1,2} was reported by Baeyer during the course of his classic researches on indigo. In the presence of cold concentrated sulfuric acid, **8a** and **8b** cyclise to the corresponding isatogens (**9a, b**) in good yield. In contrast, under the same conditions **8c** gives a mixture of isatin (**10**) and 1-hydroxyisatin (**11**).¹¹ The latter is theoretically tautomeric with 2-hydroxyisatogen (**12**), but no experimental evidence has yet been presented that would support such tautomerism.

⁶ G. R. Delpierre and M. Lamchen, *Q. Rev., Chem. Soc.* **19**, 329 (1965).

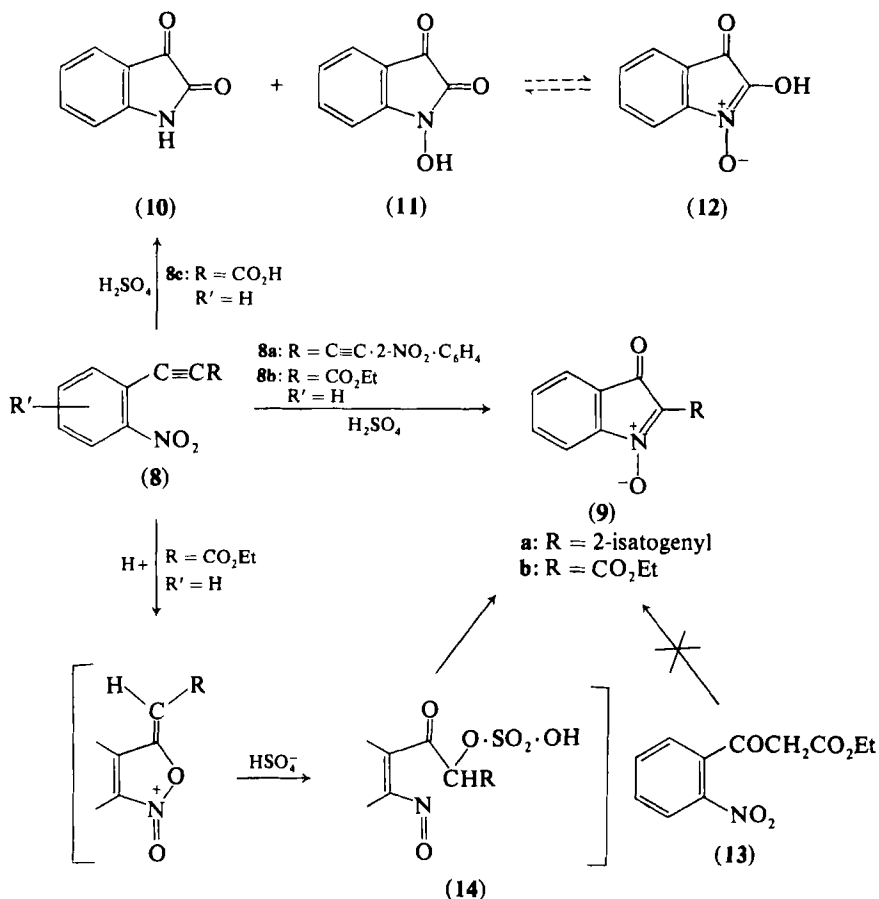
⁷ C. C. Bond and M. Hooper, *J. Chem. Soc. C*, 2453 (1969).

⁸ J. W. Robertson, Ph.D. Thesis, C.N.A.A., Sunderland Polytechnic, 1973.

⁹ R. Danieli, G. Maccagnani, and F. Taddei, *Bolletino* **26**, 45 (1968).

¹⁰ P. Pfeiffer, R. Fritsch, W. Halberstadt, G. Kirchhoff, J. Kleber, and P. Wittkop, *Ann.* **411**, 72 (1916).

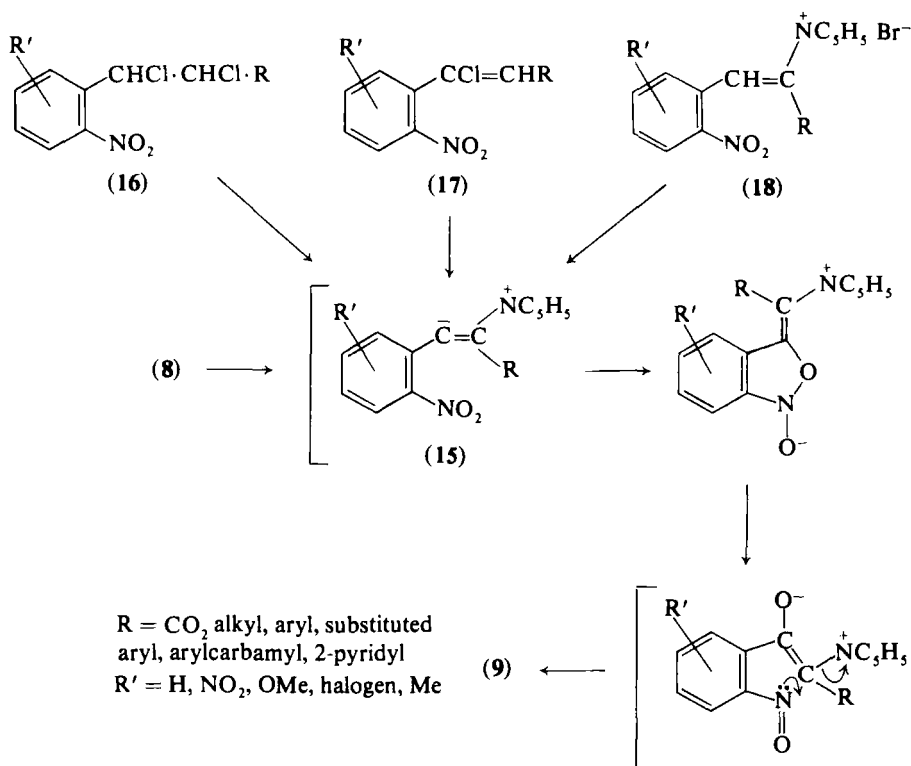
¹¹ A. Baeyer, *Ber. Deut. Chem. Ges.* **8**, 2554 (1880).



As a result of subsequent experiments, Baeyer¹¹ suggested that the first step in the cyclization of **8b** involves hydration of the triple bond to give ethyl 2-nitrobenzoate (**13**) followed by intramolecular cyclization to the isatogen (**9b**). This possibility was rejected when it was found that **13** in cold concentrated sulfuric acid failed to yield any of the expected isatogen. The only identifiable product was 2-nitrobenzoyl-acetic acid formed by hydrolysis of the ester.¹² Loudon and Tennant⁴ assumed that cyclization involved direct interaction between the nitro group and the acetylenic side chain to give a sulfate complex (**14**) (cf. Scheme 1). This reaction has not been investigated further, and later workers have chosen to use a more convenient cyclizing reagent (Sections II.A, 1, b-d).

¹² A. Baeyer, *Ber. Deut. Chem. Ges.* **15**, 2705 (1882).

b. *Pyridine and Sunlight*. When exposed to sunlight, pyridine (less commonly quinoline) solutions of a variety of 2-nitrophenylacetylenes (**8**: R = CO₂, alkyl, aryl, substituted aryl, or 2-pyridyl; R' = H, NO₂) give the corresponding isatogens in fair to moderate yields.^{10, 13, 93} Huisgen¹⁴ suggested the following general reaction mechanism (Scheme 1) in which the betaine **15** is a key intermediate. This same betaine is also an intermediate in the formation of isatogens from nitrostilbene dichlorides (**16**), μ -chlorostilbenes (**17**) (Section II,A,2), and styryl-pyridinium salts (**18**) (Section II,A,3). The mechanism seems reasonable but lacks experimental support, since none of the proposed intermediates have been isolated or trapped.



SCHEME 1

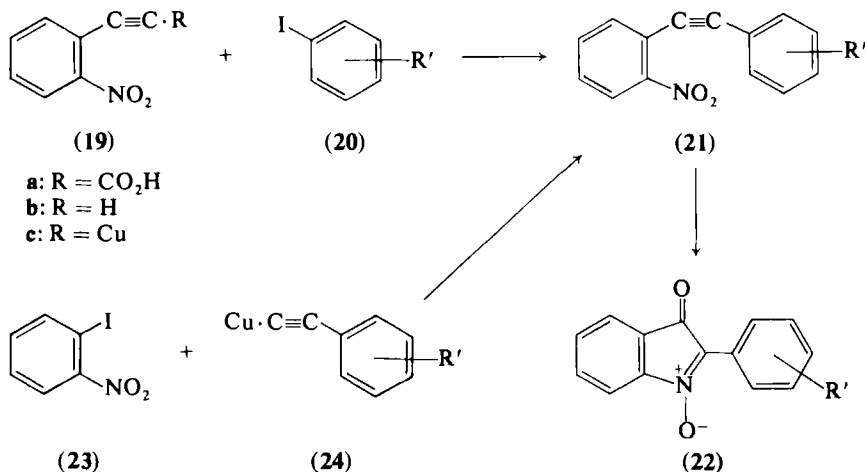
c. *Pyridine and Heat*. The cyclization of 2-nitrophenylacetylenes by heating in pyridine has not been described in the literature to any large extent, although the conversion of methyl and ethyl 2-nitrophenyl-

¹³ P. Ruggli, E. Caspar, and B. Hegedüs, *Helv. Chim. Acta* **20**, 250 (1937).

¹⁴ R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **2**, 565 (1963).

propiolates into the corresponding isotogens has been effected in good yield under these conditions.^{8,15}

Castro and Stephens¹⁶ developed a method for the preparation of unsymmetrical disubstituted acetylenes, which involves the reaction of copper(I) acetylides with aromatic iodo compounds. Bond and Hooper⁷ extended this route to the preparation of 2-arylisatogens (22). 2-Nitrophenylpropionic acid (19a) is readily decarboxylated to the acetylene (19b), which on treatment with copper(I) chloride gives 19c. The reaction of 19c with substituted aromatic iodo compounds (20) gives the corresponding acetylenes (21), which subsequently cyclize to the isotogens (22). The alternative route (23 + 24 → 21) has been little used.¹⁷



The reaction (19 + 20 → 22) is influenced by both steric and electronic factors and does not take place when acidic groups are present in the iodo compound.

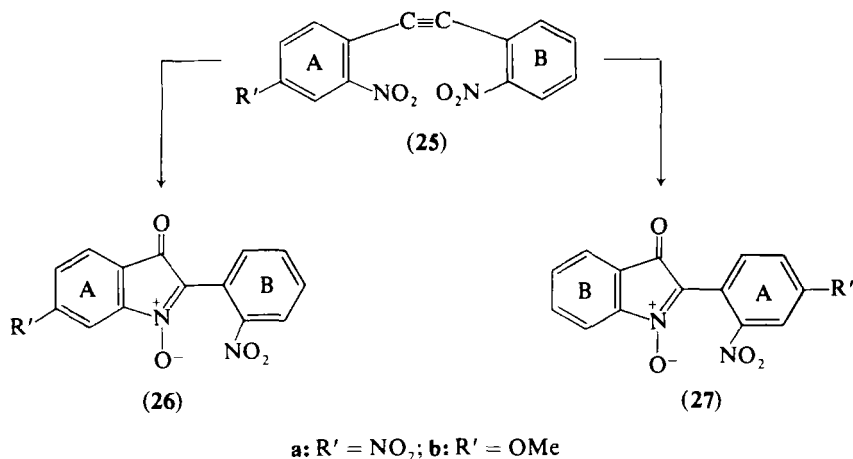
The influence of steric factors is indicated by the fact that the intermediate tolans are isolable only when ortho substituents are present (21: R' = ortho substituent). In all other cases cyclization to the isotogen takes place under the reaction conditions. The tolans (21: R' = ortho substituent) are usually cyclized by further heating in pyridine. In more difficult cases, cyclization requires irradiation of a pyridine solution or heating under reflux with nitrosobenzene in chloroform solution (Section II,A,1,d).

¹⁵ E. R. Needham and W. H. Perkin, *J. Chem. Soc.*, 148 (1904).

¹⁶ C. E. Castro and R. D. Stephens, *J. Org. Chem.* **28**, 2163 (1963).

¹⁷ J. E. Bunney, Ph.D. Thesis, University of London, 1970.

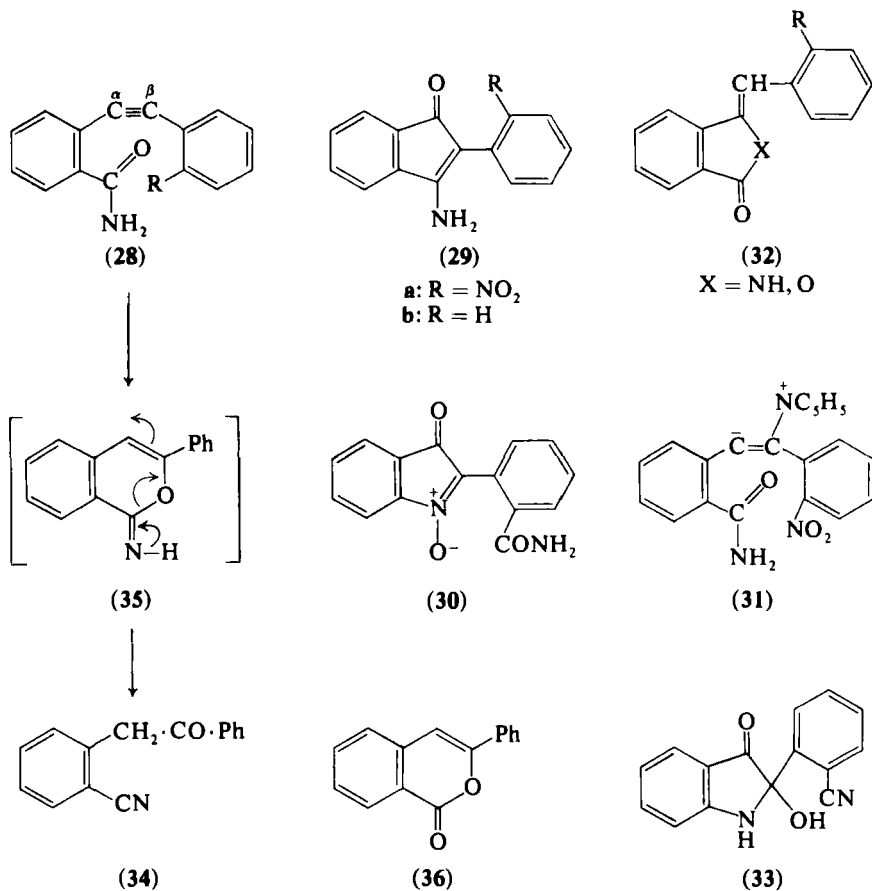
The electronic effects of substituent groups are important in determining the direction of cyclization of the intermediate tolans.⁷ When **25a** was cyclized, by heating in pyridine, only **26a** was formed; there was no trace of the other possible isomer (**27a**). In contrast, **25b** cyclizes exclusively to **27b**. A similar result was obtained with **25** ($R' = 3\text{-OMe}$) which gave only **27** ($R' = 3\text{-OMe}$). These observations support Huisgen's proposed mechanism (Scheme 1), in which the intermediate betaine (**15**) has a negative charge on the carbon atom adjacent to the phenyl ring bearing the more strongly electron-withdrawing substituent, i.e., ring A in **25a** and ring B in **25b**. Subsequent cyclization then proceeds via the ortho nitro group attached to the same phenyl ring. It is not possible, therefore, to prepare isatogens such as **27a** by this route.



A second factor that influences the course of the reaction is the presence in the molecule of other groups that can participate in an intramolecular cyclization reaction. In pyridine, the tolan **28a** preferentially cyclizes, through the carboxamide group, to the aminoindenone (**29a**): only small amounts of both the isatogen (**30**) and the indolinone (**38**) were formed. The reaction between copper(I) phenylacetylide, and 2-iodobenzamide gave a high yield of the indenone **29b**.⁷ The reaction may possibly proceed by an intermediate betaine (**31**) analogous to **15** (Scheme 1). When **28a** was heated in xylene, no isatogen was formed; the phthalimidine (**32b**: $X = \text{NH}$) was formed together with the indolone hydrate (**33**), which was identified from analytical and spectroscopic data only. The reaction through **28b** gave the indenone (**29b**), together with the phthalimidine (**32b**: $X = \text{NH}$) and the deoxybenzoin **34**.¹⁸

¹⁸ C. C. Bond, Ph.D. Thesis, C.N.A.A. Sunderland Polytechnic, 1969.

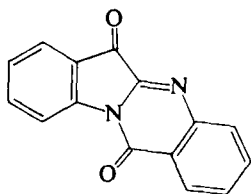
These reactions involve attack both at the α -acetylenic carbon atom by the carboxamide nitrogen atom, giving **32a,b** ($X = NH$), and at the β -acetylenic carbon atom by the carboxamide oxygen atom (**35**), leading to **34**.¹⁸ 2-Carboxytolan reacts in a similar manner to give **32b** ($X = O$) and **36**.^{18a,b}



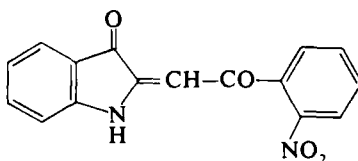
The attempted reaction of 4-iodobenzoic acid with **19c** did not yield the expected tolan or isatogen. Only trace amounts of anhydroisatin- α -anthranilide (**37**) and the indolinone **38** (Section II,A,1,d) were isolated.⁷ Both these products arise from the reactions of two molecules of **19b**, which would be formed by the action of acids on **19c**. Although **37** was unequivocally identified, it is difficult to propound a reasonable mechanism for its formation.

^{18a} C. E. Castro and R. D. Stephens, *J. Org. Chem.* **28**, 3313 (1963).

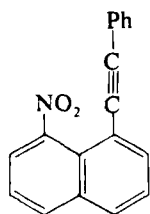
^{18b} R. L. Letsinger, E. N. Oftedahl, and J. R. Nazy, *J. Am. Chem. Soc.* **87**, 742 (1965).



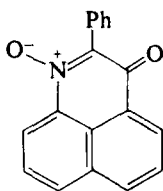
(37)



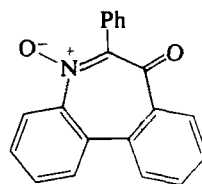
(38)



(39)



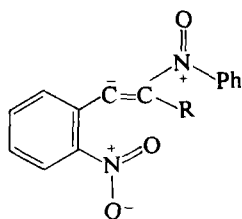
(40)



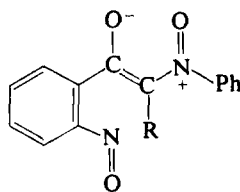
(41)

The intramolecular cyclization of a nitro group with a triple bond has been extended to the synthesis of six- and seven-membered ring compounds analogous to isatogens. Thus, the reaction of the acetylene group with the nitro group in **39** yields 2-phenyl-3-oxobenzo[de]quinoline *N*-oxide (**40**), and 6-phenyl-7-oxodibenz[*b,d*]azepine *N*-oxide (**41**) is similarly prepared from the corresponding biphenyl derivative.¹⁹

d. *Nitrosobenzene and Chloroform*. Alessandri^{20,21} and Ruggli¹³ found that chloroform solutions of 2-nitrophenylacetylenes in the presence of nitrosobenzene yield isatogens even in the absence of light. The reactions take several days for completion in the cold, but the time



(42)



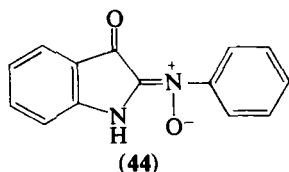
(43)

R = aryl, CO₂ alkyl

¹⁹ C. C. Leznoff and R. J. Hayward, *Can. J. Chem.* **49**, 3596 (1971).

²⁰ L. Alessandri, *Gazz. Chim. Ital.* **58**, 738 (1928).

²¹ L. Alessandri, *Gazz. Chim. Ital.* **58**, 551 (1928).

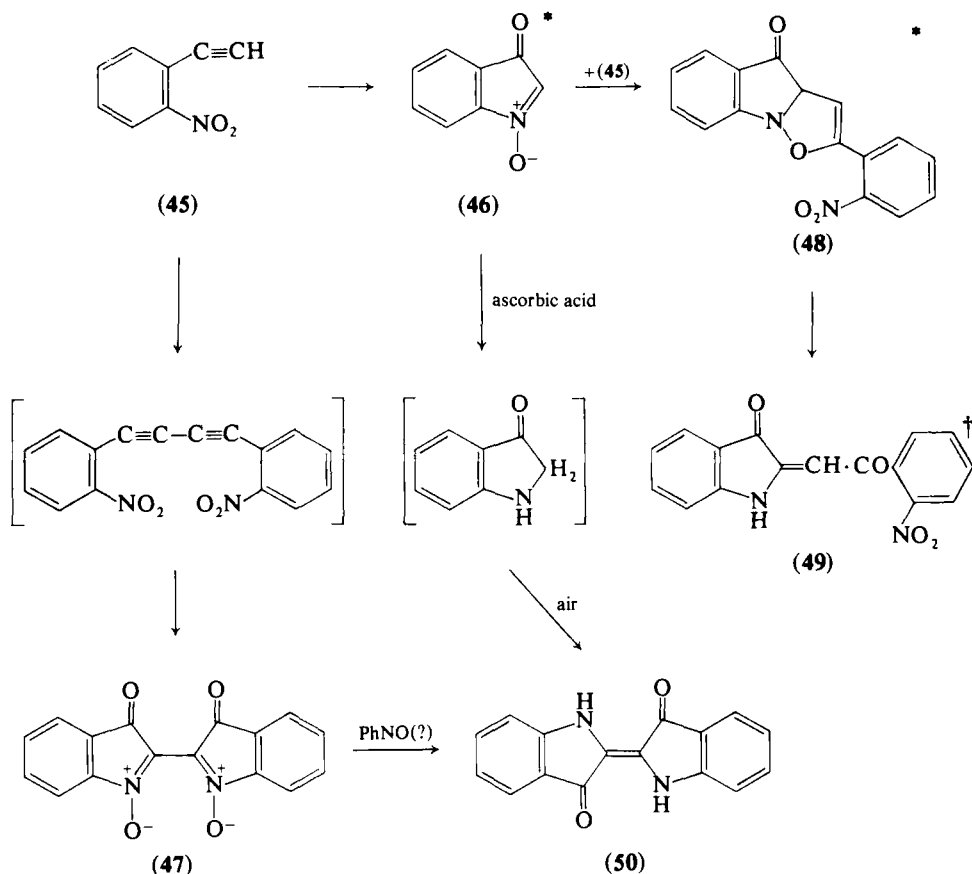


is reduced to 2 hours by heating under reflux. Patterson²² suggested a mechanism, analogous to that proposed by Huisgen (Scheme 1), involving as intermediates the betaine **42** and structure **43**.⁴ The quantitative recovery of nitrosobenzene from some of these reactions supports these proposals.¹⁸

Early workers^{20, 21, 23} found that the reaction of 2-nitrophenylacetylene (**45**) with nitrosobenzene failed to give the parent isatogen. They claimed to have isolated and identified a number of different products from the reaction depending on the nature of the solvent used. Thus, in acetic acid the reaction yielded a compound claimed to be 1-hydroxyisatin (**11**), but in ether diisatogen (**47**) was the major product. From the reaction in benzene solution, **47**, a red compound provisionally identified as the nitrone **44**, and an unidentified white compound were obtained. Using preparative layer chromatography, a separation technique unknown to the earlier workers, Bond carried out a detailed study of these reactions and showed some of the earlier conclusions to be incorrect.¹⁸ The reactions in both ether and benzene give the same five products, none of which were 1-hydroxyisatin. Two of these were identified as diisatogen (**47**) and indigo (**50**). The latter was present in only very small quantities. Two stable unknown compounds, one red and one colorless, were also isolated together with an unstable purple compound. The relative yields of these compounds varied with the reaction times, indicating the possibility that some of them might be intermediates in the overall reaction. The red compound was identified, from spectroscopic and synthetic evidence, as the previously unknown 2-(2-nitrobenzoyl)-methyleneindolin-3-one (**49**), not **44**. The colorless compound was identical with that isolated by Alessandri;^{20, 21} from spectroscopic evidence and its ready conversion into the isomeric indolinone **49**, it was formulated as the isoxazoloindole **48**.⁷ The purple compound, isolated as a crude product, was formulated as the parent isatogen (**46**) on the basis of spectroscopic evidence and its reduction by ascorbic acid to indigo (Section III,B).^{7, 18} The overall reaction sequence is shown in Scheme 2.

²² D. A. Patterson, Ph.D. Thesis, University of London, 1966.

²³ L. Alessandri, *Gazz. Chim. Ital.* **57**, 195 (1927).



SCHEME 2. * Present after 4 hours but not after 24 hours. † Amount present increases with time.

2. From Stilbenes and Their Derivatives

The addition of halogens to stilbenes (**51**) gives stilbene dihalides (**52**) in good yield. Treatment of **52** with strong base furnishes the 2-nitrophenylacetylenes (**53**), which are readily isomerized to isatogens (**55**; Sections II,A,1,a-d). The stereochemistry of **51** is important. Only the dihalides (**52**) formed from *trans*-stilbenes undergo dehydrohalogenation to **53**.^{13,24} The action of weak bases on **52** gives μ -halogenostilbenes (**54**). Both **52** and **54** yield isatogens, directly but slowly, when their pyridine (or quinoline) solutions are exposed to

²⁴ D. A. Jones, Ph.D. Thesis, University of Minnesota, 1961.

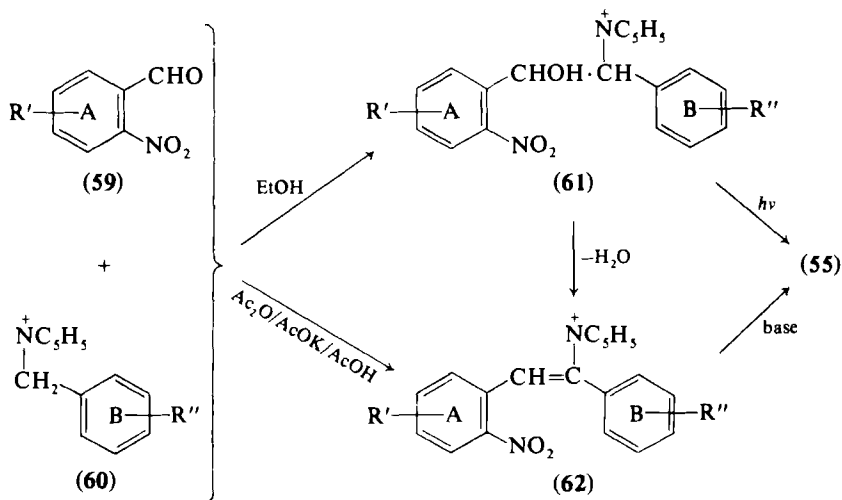
- ²⁵ P. Ruggli and A. Disler, *Helv. Chim. Acta* **10**, 938 (1927).
- ²⁶ P. Ruggli and A. Zimmerman, *Helv. Chim. Acta* **15**, 865 (1932).
- ²⁷ P. Ruggli and E. Wolff, *Helv. Chim. Acta* **19**, 5 (1936).
- ²⁸ P. Ruggli and R. Preuss, *Helv. Chim. Acta* **24**, 1345 (1941).
- ²⁹ P. Ruggli, A. Schmid, and O. Zimmerman, *Helv. Chim. Acta* **7**, 1328 (1934).
- ³⁰ J. S. Splitter and M. Calvin, *J. Org. Chem.* **20**, 1086 (1955).
- ³¹ M. Hooper, D. A. Patterson, and D. G. Wibberley, *J. Pharm. Pharmacol.* **17**, 734 (1965).

conjugation (**51**: R = styryl, 4-phenylbuta-1,3-dien-1-yl; R' = H) also cyclize to isatogens when solutions in benzene containing iodine are exposed to sunlight.¹⁹ The mechanism of these reactions is uncertain. The original proposals³⁰ have been criticized by Huisgen¹⁴ and modified by Patterson.²²

Bakke³² has recently reported that 2-nitrophenylethanols (**57**), under acid conditions, give varying amounts of stilbenes (**51**), isatogens (**55**), anthranils (**58**), and other products. 2-Nitrotolan (**53**: R = Ph; R' = H) also gives the corresponding isatogen, in low yield (cf. Section II,A,1,c), together with the anthranil. Isatogens isomerize to anthranils under acid conditions (Section III,A,1). These reactions are summarized in Scheme 3.

3. From Pyridinium Ethanols and Vinylpyridinium Salts

2-Nitrobenzaldehydes (**59**) and benzylpyridinium salts (**60**) react to form pyridinium ethanols **61**. Kröhnke and co-workers found that irradiation of **61**, with sunlight or ultraviolet light, gives 2-arylisatogens (**55**: R = aryl and substituted aryl) and that the same isatogens are also formed by the action of base on vinylpyridinium salts (**62**), which may be prepared directly or by dehydration of **61** (Scheme 4).³³⁻³⁵ The



R = aryl, substituted aryl

SCHEME 4

³² J. M. Bakke, *Acta Chem. Scand., Ser. B* **29**, 1063 (1975).

³³ F. Kröhnke and M. Meyer-Delius, *Chem. Ber.* **84**, 932 (1951).

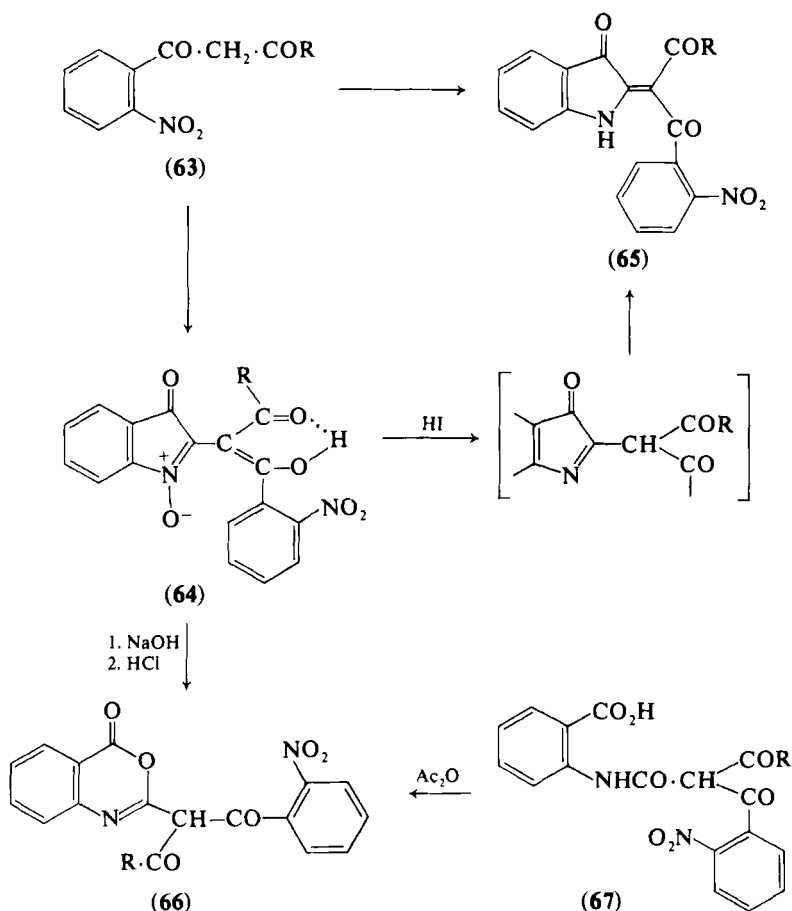
³⁴ F. Kröhnke and I. Vogt, *Chem. Ber.* **85**, 376 (1952).

³⁵ F. Kröhnke and I. Vogt, *Chem. Ber.* **86**, 1500 (1953).

reaction does not involve 2-nitrotolan intermediates, since they do not yield isatogens under these conditions. Isatogens are formed, probably via a betaine intermediate (**15**, Scheme 1), only when ring A of **61** or **62** contains an ortho nitro group. It should therefore be possible to prepare by this route isatogens that are not available by the isomerization of 2-nitrotolans, e.g., **55** ($R = 2,4$ -dinitrophenyl; $R' = H$; Section II,A,1,c).

4. Miscellaneous Intramolecular Cyclization Reactions

2-Nitrobenzoylacetone (**63a**) and the related 2-nitrobenzoylacetates (**63b,c**) undergo self-condensation, with cyclodehydration to isatogens

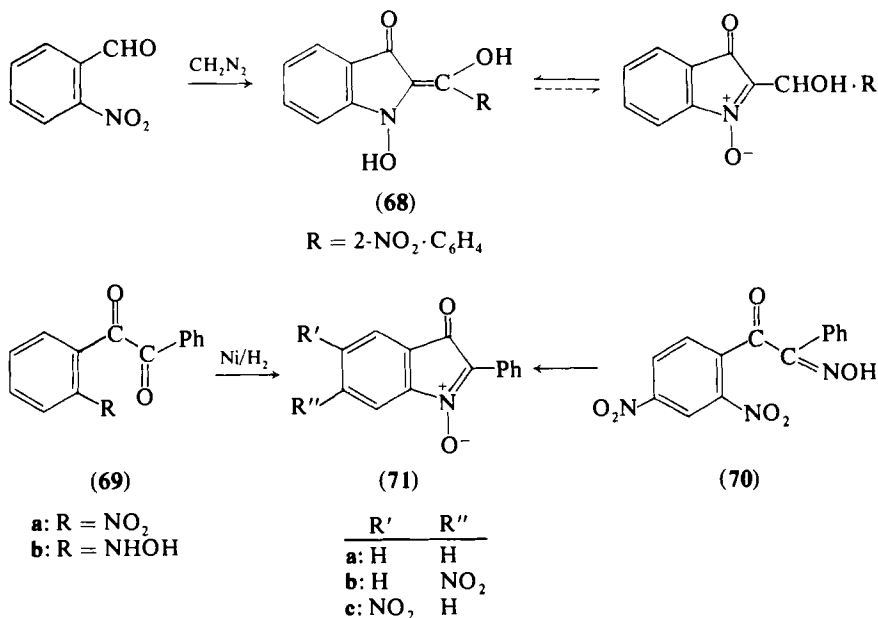


a: $R = Me$
 b: $R = OMe$
 c: $R = OEt$

SCHEME 5

(64) and indolinones (65) in the presence of sodium bicarbonate or piperidine.³⁶ From infrared spectroscopic data, **64a–c** exist in the intramolecular hydrogen-bonded form shown. Treatment of **64b, c** with strong base followed by acidification gives benzoxazinones (66). The structure of these last compounds was confirmed by their unambiguous synthesis from the corresponding anthranilides (67). Deoxygenation of **64** with hydriodic acid⁵ in acetic acid gives indolones that preferentially exist as the tautomeric indolinones (65)⁴ (Scheme 5).

Until recently these were the first examples of isatogens in which an aryl ring is not directly attached to the 2-position of the indole ring except for the isatogenic esters and the compound **68** isolated in very low yield from the reaction of 2-nitrobenzaldehyde with diazomethane and claimed to exist as the *N*-hydroxy tautomer.³⁷ However, in all these cases the carbon atom attached to the 2-position of the isatogen molecule is sp^2 hybridized, allowing extended conjugation of the isatogen ring and the side chain in the 2-position.



Reductive cyclization of 2-nitrobenzil (**69a**) is reported to give the isatogen **71a**, via the intermediate hydroxylamino compound **69b**.³⁸ Little isatogen would be expected under these conditions in view of their

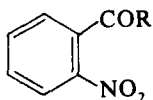
³⁶ M. Hooper and D. G. Wibberley, *J. Chem. Soc. C*, 1596 (1966).

³⁷ L. Capuano, *Chem. Ber.* **98**, 3187 (1965).

³⁸ P. Ruggli and B. Hegedüs, *Helv. Chim. Acta* **22**, 147 (1939).

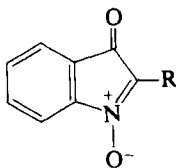
rapid reduction to indolones and indoxyls (Section III,B). The reported preparation of 6-nitro-2-phenylisatogen (**71b**) from the benzil oxime (**70**) after treatment with sodium ethoxide³⁹ is also surprising since isatogens are rapidly degraded by strong bases (Section III,A,1). 5-Nitro-2-phenylisatogen (**71c**) is one of the products arising from the reaction of dinitrogen tetroxide with tolan.⁴⁰

The decomposition of 2-nitrobenzoylacetone (**72a**) to isatin (**74a**) is considered to proceed via 2-acetylisatogen (**73a**).⁴ 2-Acylisatogens were unknown until recently, when Robertson⁸ reported the preparation of **73b** from the corresponding acetylene. 1-Hydroxyisatin (**74b**), formulated as the tautomeric 2-hydroxisatogen (**73c**) (Section II,A,1,a) is postulated as an intermediate in the decomposition of 2-nitrophenacyl chloride (**72b**)⁴¹ and 2-nitrobenzoyldiazomethane (**72c**).⁴²



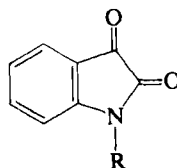
(72)

- a: R = CH₂COMe
b: R = CH₂Cl
c: R = CHN₂



(73)

- a: R = COMe
b: R = CPh
c: R = OH



(74)

- a: R = H
b: R = OH

B. OXIDATION OF 2-SUBSTITUTED INDOLES

Current studies^{43,44} show that a range of isatogens can now be prepared in good yield by the oxidation of 2-substituted 1-hydroxyindoles and 2-substituted indolines with perbenzoic acids. Until this work, 2-phenylisatogen was reported as only a minor product from a number of reactions of 2-phenylindole derivatives with a variety of oxidizing agents.

³⁹ G. Bishop and O. L. Brady, *J. Chem. Soc.*, 810 (1926).

⁴⁰ K. N. Campbell, J. Shavel, and B. K. Campbell, *J. Am. Chem. Soc.* **75**, 2400 (1953).

⁴¹ J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 4268 (1963).

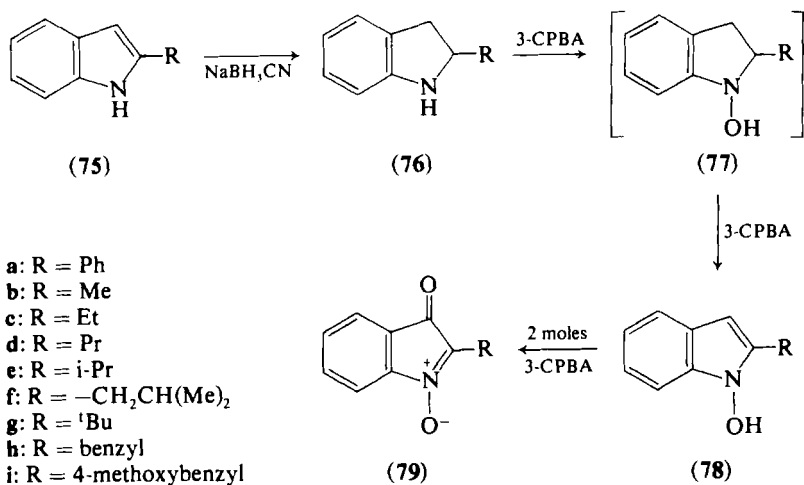
⁴² F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.* **60**, 1364 (1927).

⁴³ T. H. C. Bristow, H. E. Foster, and M. Hooper, *J. Chem. Soc., Chem. Commun.*, 674 (1974).

⁴⁴ S. P. Hiremath and M. Hooper, unpublished results (1976).

1. Oxidations with Perbenzoic Acids

2-Substituted indoles (**75**) are reduced to the corresponding indoles (**76**) by a variety of reagents; sodium cyanoborohydride is particularly suitable.⁴³⁻⁴⁵ The oxidation of **76** by 3-chloroperbenzoic acid (3-CPBA) provides a general route to isatogens (**79**), particularly the previously unknown 2-alkylisatogens.^{43,44} Robertson⁸ had earlier prepared the unstable isatogen (**79**; $R = \text{CH}(\text{OMe})_2$), which is the first example of an isatogen with an sp^3 hybridized carbon atom directly attached to the 2-position. The reactions with 3-CPBA take place readily, at or below room temperature, and give isatogens in good yields. Overall, four equivalents of the peracid are consumed in the reaction. A mechanism involving *N*-hydroxylation of the indoline (**77**) followed by dehydrogenation to the 1-hydroxyindole (**78**) and further oxidation to the isatogen (**79**) has been proposed.⁴³ The mechanism is supported by the known selective *N*-hydroxylation of secondary amines by 3-CPBA,⁴⁶ the detection of **78a** in the reaction mixture and the almost quantitative oxidation of **78a** to **79a** by 4-nitroperbenzoic acid.⁴⁷



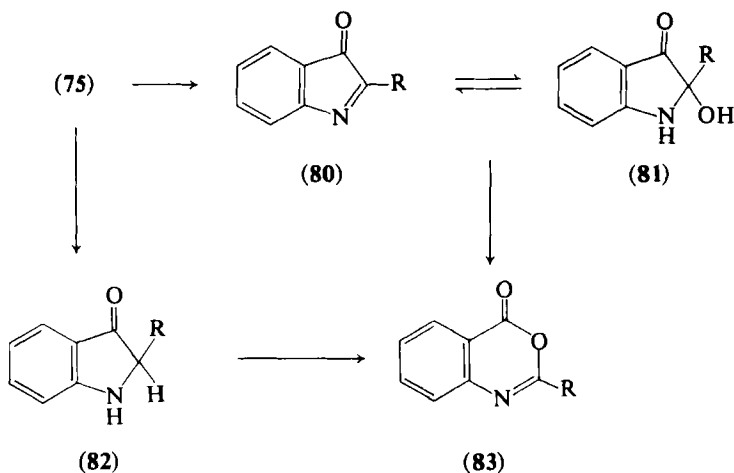
Indoles (**75**), indolones (**80**), indolone hydrates (**81**), and indoxyls (**82**) could theoretically be formed in these reactions by loss of water from **77**, or by preferential oxidation of the indole or indoline at the 3-

⁴⁵ G. W. Gribble, P. D. Lord, J. Skofnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.* **96**, 7812 (1974).

⁴⁶ A. H. Beckett, R. T. Coutts, and F. A. Ogunbona, *J. Pharm. Pharmacol.* **25**, 190 (1973).

⁴⁷ C. C. Bond and M. Hooper, *Synthesis*, 443 (1974).

position. Indoles (**75**)^{43,44,48} and indoxyls^{43,44} are oxidized under these conditions by monoperphthalic acid,⁴⁸ to indolones, indolone adducts, and benzoxazines (Section IV,A,2).^{43,48-50} There is no suitable method for the direct oxidation of indolones (**80**) to isatogens (**79**).⁵⁰ The absence of **75**, and **80-83** clearly indicates that 3-CPBA under these conditions oxidizes indolines preferentially at the 1-position. When this position is blocked, oxidation takes place less readily at the 3-position.⁴⁴ Indoles do not have a basic nitrogen center and undergo initial oxidation at the 3-position without ring opening.



The 1-hydroxyindoles (**78**: R = Ph, 2-pyridyl, CO₂Me) are rapidly oxidized by 4-nitroperbenzoic acid to the corresponding isatogens (**79**).^{18,47} The exploitation of this synthesis awaits the development of efficient general syntheses of **78**. Recently an electrochemical method has been described.^{51,52}

2. Miscellaneous Oxidation Reactions

Small amounts of 2-phenylisatogen (**79a**) are formed, together with a number of dimeric indole compounds, as a result of the oxidation of 1-hydroxy-2-phenylindole (**78a**) with a variety of oxidizing agents (Scheme 6).

⁴⁸ E. Braudeau, S. David, and J-C. Fischer, *Tetrahedron* **30**, 1445 (1974).

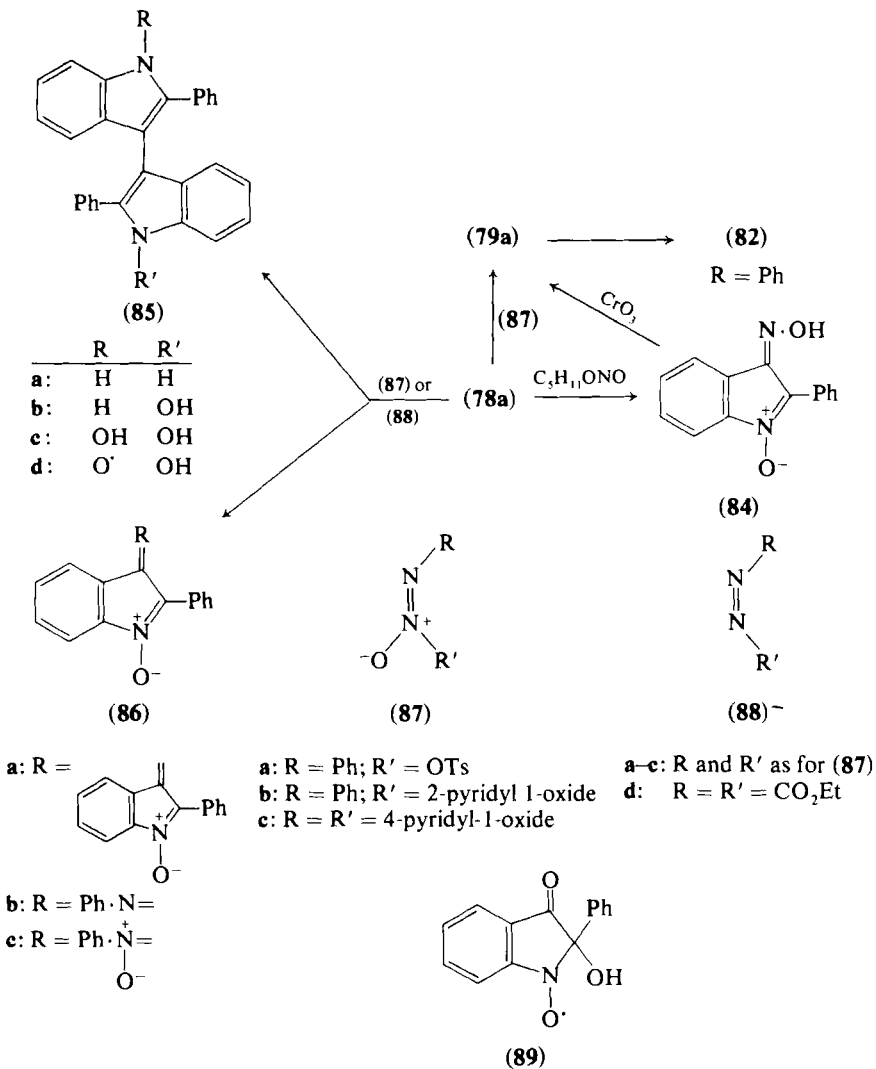
⁴⁹ H. S. Ch'ng, Ph.D. Thesis, University of London, 1971.

⁵⁰ R. J. Richmann and A. Hassner, *J. Org. Chem.* **33**, 2548 (1968).

⁵¹ R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 3040 (1973)

⁵² R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 121 (1974).

In 1906 Angeli and Angelico⁵³ treated **78a** with amyl nitrite under alkaline conditions. They isolated the oxime (**84**), which on treatment with chromic acid gave **79a**. They claimed to have identified the isatogen by its reduction to the unstable indoxyl **82** ($R = Ph$), which has subsequently been shown to give dimeric compounds (Section III,B).



SCHEME 6

⁵³ A. Angeli and F. Angelico, *Atti. R. Accad. Lincei* **13** I, 257 (1906) [*Chem. Zentr.* **1**, 732 (1907)].

Ajello⁵⁴ suggested that amyl nitrite acts solely as an oxidizing agent under neutral conditions. He positively identified **79a** among the products of the reaction, but the chemistry of the other reaction products remains uncertain. The autoxidation of **78a** in ethanolic sodium ethoxide is claimed to give **79a** together with the dimeric compounds (**85a,b**).⁵⁵ The isatogen would not be stable under these conditions (Section III,A,1). Autoxidation in the presence of copper(II) or iron(III) ions also gives **79a** together with the dimeric 1-hydroxyindole (**85c**) and the bisnitron (**86a**).⁵⁵ Diimide oxides (**87a-c**) also oxidize **78a** to **79a**, the dimeric indole (**85a**), and the isatogen derivative (**86b**).⁵⁶ Diimides (**88**), which are also oxidizing agents, react with **78a** to give **85c, d** together with **86a** and **86b**.⁵⁶ The interrelated redox systems, diimide oxides, diimides, and hydrazines are analogous to those of isatogens, indolones, and indoxyls (Section III,B). Lead tetraacetate also oxidizes **78a** to **79a**⁵⁷ and the free radical **89**⁵⁸ which is also formed when the oxidizing agent is lead dioxide in the absence of air.⁵⁹ The bisnitron **86c** on irradiation gives **79a** and azobenzene by an intramolecular transfer of oxygen. A number of other products are formed.⁶⁰

III. Chemical Properties of Isatogens

Isatogens exhibit reactions characteristic of both nitron and carbonyl groups. The carbon atom of the nitron group is much the more reactive site, generally behaving as an electron-deficient center. The reactivity at this site (relative to the 2-phenyl compound) is increased by electron-withdrawing groups, such as 2-pyridyl or alkoxy carbonyl, and decreased by electron-releasing groups, such as 4-methoxyphenyl. Reactivity is also enhanced when conjugation with the 2-substituent, resulting in delocalization of the positive charge, is not possible, i.e., 2-alkylisatogens are more reactive than 2-aryl or 2-alkoxy carbonyl isatogens. Some reactions, particularly reduction, involve either sequential or simultaneous attack by the reagent at the nitron and carbonyl groups. In contrast, nucleophilic attack at the carbonyl group takes place very rarely and never exclusively.

⁵⁴ T. Ajello, *Gazz. Chim. Ital.* **69**, 646 (1939) [*CA* **34**, 3734 (1940)].

⁵⁵ L. Marchetti and V. Passalacqua, *Ann. Chim. (Rome)* **57**, 1251 (1967).

⁵⁶ M. Colonna and P. Bruni, *Gazz. Chim. Ital.* **99**, 885 (1969).

⁵⁷ M. Colonna and P. Bruni, *Gazz. Chim. Ital.* **95**, 1172 (1965).

⁵⁸ G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer, and R. Blankespoor, *J. Am. Chem. Soc.* **92**, 2762 (1970).

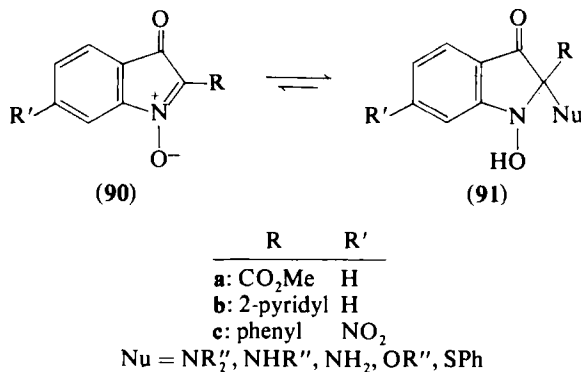
⁵⁹ P. Bruni and M. Colonna, *Tetrahedron* **29**, 2425 (1973).

⁶⁰ M. Colonna and M. Poloni, *Ann. Chim.* **63**, 287 (1973).

A. REACTIONS AT THE NITRONE GROUP

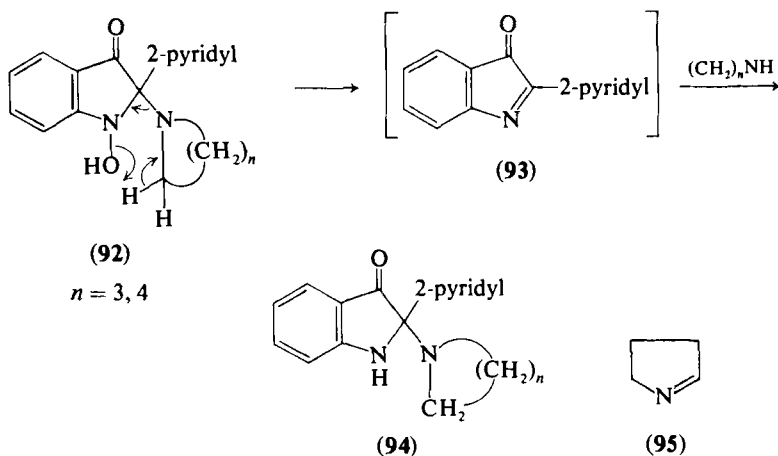
1. *Nucleophilic Addition and Subsequent Reactions of the Adducts*

Aliphatic amines, alcohols, and thiophenol add reversibly to the nitron group of the more reactive isatogens (**90**) to give unstable adducts (**91**). The reactions can be followed by ultraviolet (UV) spectroscopy (Section VI,A). The adducts frequently undergo further intramolecular reactions to give more stable compounds. The presence of an ester group, as in **90a**, provides another site for nucleophilic attack leading to further possibilities for side reactions and products. In order to avoid such complications most of these reactions have been studied using **90b**.

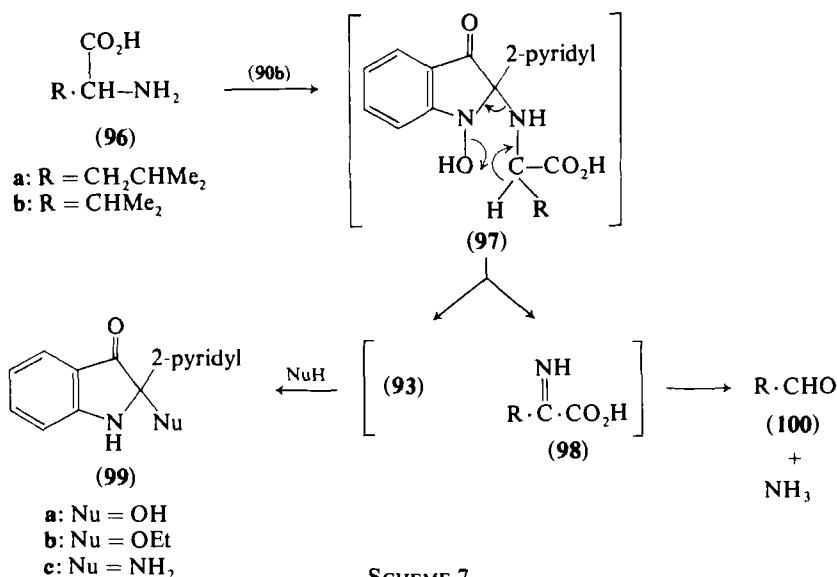


The reactions involving 2-(2-pyridyl)isatogen (**90b**) and amines or amine derivatives have been most thoroughly studied. At room temperature ethyl acetate solutions of **90b** and piperidine, in a 10 *M* excess, deposit green crystals of the adduct (**92**). The adduct readily breaks down into its constituents in a variety of organic solvents and on silica gel plates. When the reaction is heated under reflux, the yellow indolone adduct (**94**; *n* = 4) is formed (Section V,A,1).⁶¹ Overall the reaction may be considered to involve reduction of the isatogen to the indolone (**93**) followed by formation of the piperidine adduct (**94**; *n* = 4). The reaction could proceed by several possible reaction pathways. The reaction mixture gave no detectable electron spin resonance (ESR) signal, so free-radical intermediates were judged to be unlikely. The reaction of **90b** with pyrrolidine gave a compound tentatively identified as Δ^1 -pyrroline (**95**) together with the corresponding indolone adduct (**94**; *n* = 3).

⁶¹ D. A. Patterson and D. G. Wibberley, *J. Chem. Soc.*, 1706 (1965).



The reaction mechanism has been further investigated using α -amino acids (96).^{8,62} In aqueous ethanol these amine derivatives exist as zwitterions in equilibrium with varying amounts of the uncharged molecules,^{62a} which are oxidatively deaminated, via unstable imino acids (98), to stable detectable aldehydes (100). When ethanolic solutions of 2-(2-pyridyl)isatogen (90b) and 96a or 96b are refluxed under nitrogen,



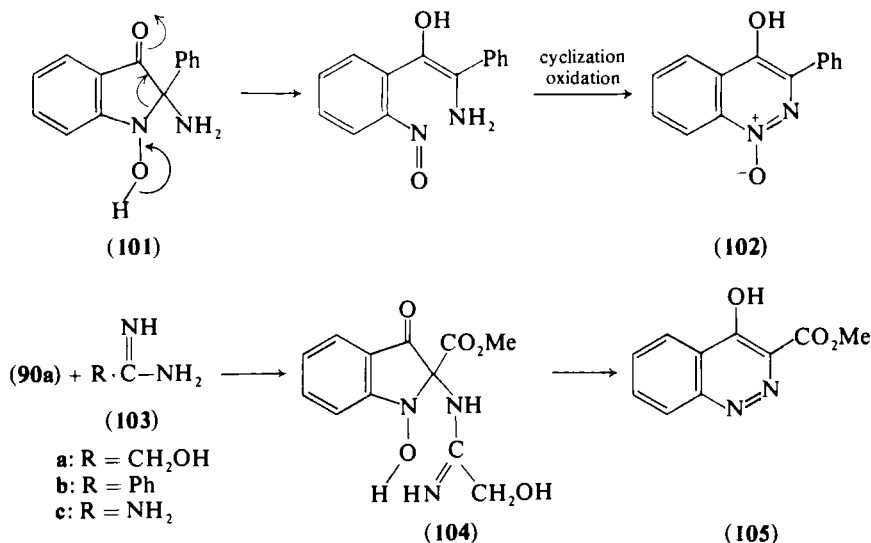
SCHEME 7

⁶² M. Hooper and J. W. Robertson, *Tetrahedron Lett.*, 2139 (1971).

^{62a} J. T. Edsal and M. H. Blanchard, *J. Am. Chem. Soc.* **55**, 2337 (1933).

the products of the reaction are the water, ethanol, and ammonia adducts of 2-(2-pyridyl)indolone (**99a–c**) together with the corresponding aldehydes (**100a** or **b**) and ammonia. In a quantitative study of the reaction between **90b** and **96a**, the adduct **99a**, isovaleraldehyde (**100a**), and ammonia were formed in yields of 93, 87, and 70%, respectively. These observations strongly support a six-center intramolecular reaction of the initial adducts **97** (Scheme 7).⁶² Other α -amino acids and amino acid esters react more slowly. Frequently, a variety of complex, and as yet unidentified, products are formed.⁸

Ammonia under more vigorous conditions reacts with 2-phenylisatogen to give the cinnoline (**102**). A mechanism involving initial formation of the ammonia adduct (**101**), followed by ring expansion and oxidation has been proposed.⁶³ The reactions of **90a** and **b** with various amidines (**103a–c**) has been briefly investigated.¹⁷ A variety of complex reaction products arise, among which the cinnoline **105** was positively identified.⁶⁴ The reaction probably involves addition of the amidine **104** followed by a rearrangement–elimination reaction analogous to that described below (Scheme 8).



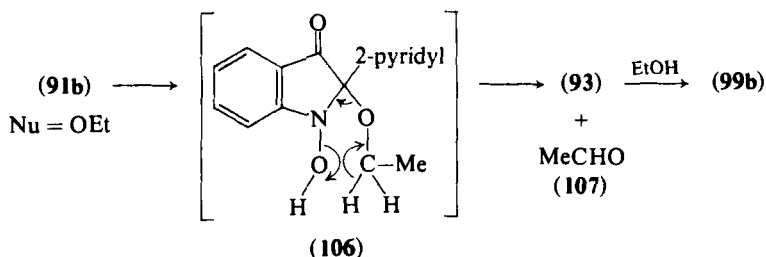
The addition of alcohols to isatogens has been less thoroughly investigated. Early workers claimed to have isolated the ethanol adduct (**91c**: Nu = OEt) by treatment of the corresponding isatogen with cold ethanolic hydrochloric acid.⁶⁵ In view of the very labile nature of these

⁶³ W. E. Noland and D. A. Jones, *J. Org. Chem.* **27**, 341 (1962).

⁶⁴ J. C. E. Simpson, *J. Chem. Soc.*, 1035 (1946).

⁶⁵ G. Heller and W. Boessneck, *Ber. Deut. Chem. Ges.* **55**, 474 (1922).

adducts and the known acid-catalyzed rearrangement of isotogens (see **119** below) this claim requires further examination. Cold ethanolic solutions of **90b** slowly lose the UV absorption characteristic of the isotogen while an absorption band associated with the indolone adduct (**99b**) gradually develops (Section VI,A). The same adduct was identified when ethanolic solutions of **90b** were refluxed under nitrogen for 4 hours.⁶⁶ This evidence suggests that alcohols are oxidized, in a similar manner to amino acids and amines via the intermediate **106**, to aldehydes (**107**).



The reaction of cold ethanolic solutions of isotogens (**108a–e**) with carbanions generated from substituted acetonitriles (**109a–d**) and piperidines leads to isoxazolines (**10**), which may further react to give isoxazolidines (**111**) and/or quinolones (**112**) (Scheme 8).^{17, 67, 68} The time of the reactions varies from 6 hours to 7 days depending on the reactivity of the isotogen and the ease of carbanion formation. The order of reactivity of the isotogens follows the expected order of nucleophilic attack at C-2: **108a** \geq **108b** > **108c** > **108d** > **108e**. The order of reactivity of the substituted acetonitriles corresponds to the ease of carbanion formation: **109a** > **109b** > **109c** > **109d**. The least reactive isotogen (**108e**) reacts only with malononitrile; it is recovered unchanged from the other reactions.

The cleanest reactions giving the highest yields (55–99%) are those between the isotogens **108a–d** and ethyl cyanoacetate (**109b**); the isoxazolines (**110**; $\text{R}' = \text{CO}_2\text{Et}$) were identified from analytical, spectroscopic, and degradative studies and shown to exist in the amino form. Simple 5-aminoisoxazol-3-ones have been shown to exist as the amino tautomers.^{69, 70} The formation of **110** ($\text{R}' = \text{CO}_2\text{Et}$) is analogous to the known intramolecular attack of the hydroxylamino oxygen atom

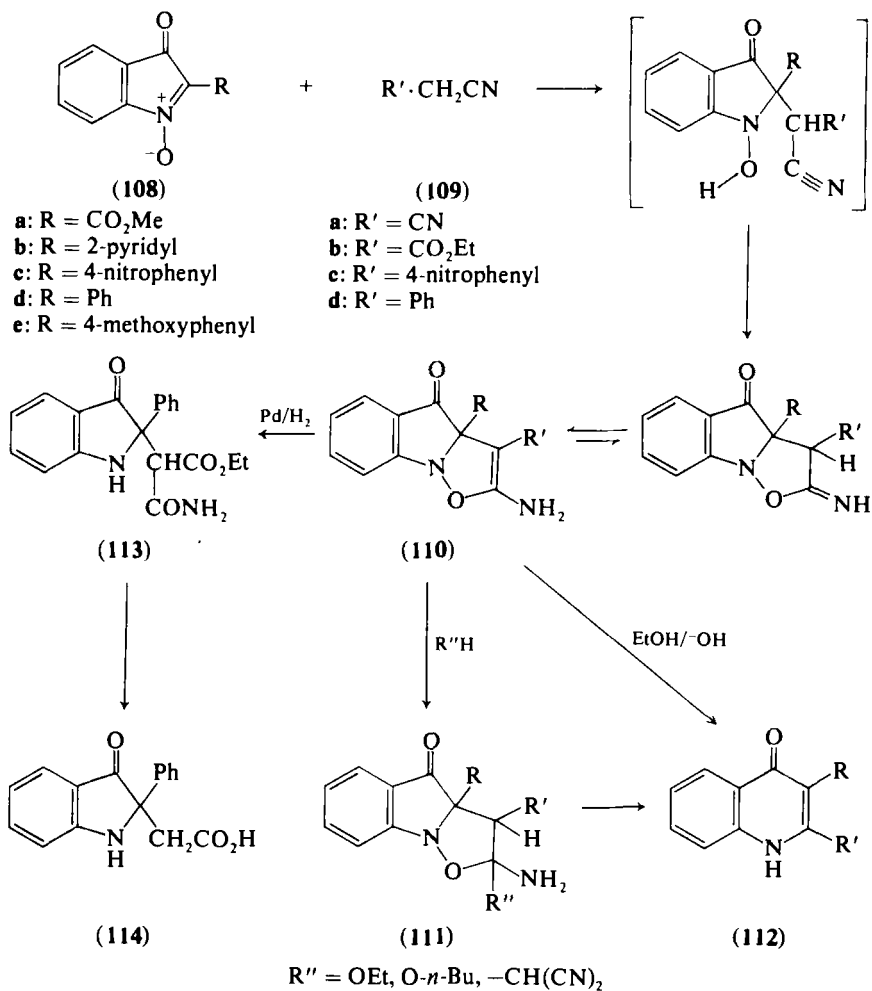
⁶⁶ R. Herbert and M. Hooper, unpublished results (1975).

⁶⁷ J. E. Bunney and M. Hooper, *Tetrahedron Lett.*, 3857 (1966).

⁶⁸ J. E. Bunney, H. E. Foster, and M. Hooper, unpublished results (1975).

⁶⁹ F. Leonard and K. Undheim, U.S. Patent 3,152,139 (1964) [*CA* **62**, 565 (1965)].

⁷⁰ C. J. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.* **26**, 4923 (1961).



SCHEME 8

on the cyanide group, which leads to the formation of isoxazolones and isoxazoles.⁷¹ The formation of quinolones (**112**) is analogous to the decomposition of isoxazolidines described below (Section III,A,2).⁷² Degradative studies were carried out on **110** (R = Ph; R' = CO₂Et). Catalytic reduction led to fission of the N—O bond and formation of the indolone adduct **113**, which was also synthesized from 2-phenylindolone (Section V,A). Hydrolysis of **113** gave the known indolinone **114**.⁷³ The

⁷¹ L. Bauer and C. N. V. Nambury, *J. Org. Chem.* **26**, 4917 (1961).

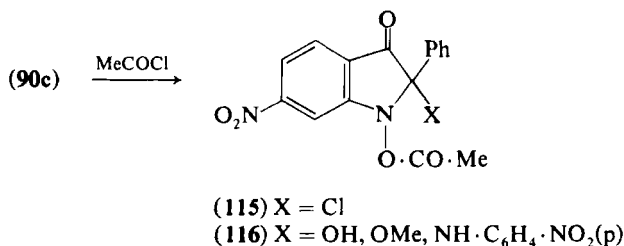
⁷² W. E. Noland and R. F. Modler, *J. Am. Chem. Soc.* **86**, 2086 (1964).

⁷³ W. E. Noland and D. A. Jones, *Chem. Ind. (London)*, 363 (1962).

addition of alcohol, **110** \rightarrow **111**, takes place readily on heating under reflux. This is in accord with the reported addition of alcohol⁷⁴ and water⁷ to the isoxazoline double bond. Treatment of **110** with sodium hydroxide in ethanol gave the corresponding quinolone (**112**; $R = Ph$; $R' = CO_2H$); see also Section III,A,2.

The remaining nitriles (**109a,c,d**) give more complex reaction mixtures from which a variety of isoxazolines (**110**), isoxazolidines (**111**), and quinolones (**112**) have been isolated by preparative layer chromatography. Reactions involving the highly reactive **109a** had to be carried out under nitrogen. The more reactive isatogens (**108a,b**) give rise to the corresponding isoxazolines (**110**), but more prolonged reaction with **108c** gives a compound identified, from spectroscopic and analytical data, as the isoxazolidine **111** ($R = 4\text{-nitrophenyl}$; $R' = CN$; $R'' = -CH(CN)_2$). Formation of this compound could take place by nucleophilic addition of **109a** across the double bond of the isoxazoline ring. A small amount of the quinolone (**112**; $R = 4\text{-nitrophenyl}$; $R' = 4\text{-nitrophenyl}$) was also isolated. Prolonged reaction (5–7 days) between **108d,e** and **109a** gives small amounts of the isoxazolidines (**111**; $R = Ph$ or 4-methoxyphenyl ; $R' = CN$; $R'' = OEt$) presumably by solvent addition to the corresponding isoxazolines. In the reactions of **109c** with **108a–c** only the corresponding isoxazolines were identified. The reaction of **109c** with **108d** gives only the corresponding quinolone, and with **108e** the isoxazolidine (**111**; $R = 4\text{-methoxyphenyl}$; $R' = 4\text{-nitrophenyl}$; $R'' = OEt$) and the quinolone (**112**; $R = 4\text{-methoxyphenyl}$; $R' = 4\text{-nitrophenyl}$). The least reactive nitrile (**109d**) reacts only very slowly with all the isatogens (**108a–d**). The known quinolone⁷⁵ **112** ($R = R' = Ph$) was isolated from the reaction of **108d** with **109d**.

In view of the very labile nature of the products of 1,3-addition to the nitrone group, the claim^{5,76} that **90c** reacts with acetyl chloride to form a "fairly stable" adduct (**115**), which undergoes further nucleophilic substitution (forming **116**) requires further investigation.

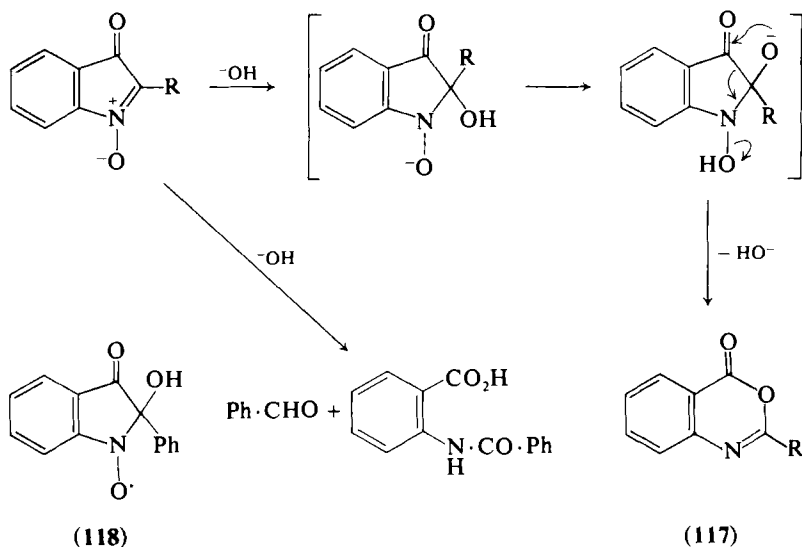


⁷⁴ R. F. Modler, personal communication (1967).

⁷⁵ "Beilsteins Handbuch der organische Chemie," Vol. 21, I, p. 236. Springer-Verlag, Berlin and New York, 1935.

⁷⁶ P. Ruggli, W. Leonhardt, and A. Bolliger, *Helv. Chim. Acta* **6**, 594 (1923).

Nucleophilic attack by hydroxide ions initially takes place at the nitron group, rearrangement giving benzoxazines (117)³⁶ (see also Scheme 5, Section II,A,4). More extensive decomposition of 2-phenylisatogen (108d) is reported to give *N*-benzoylanthranilic acid⁷⁷ and benzaldehyde.^{39, 77} A free-radical detected in a polarographic study of this reaction was at first assigned the nitroxide structure (118) but is now considered to have a ring-opened structure.^{58, 59, 78} An early report⁷⁹ that benzene is an alkaline degradation product of this reaction needs reinvestigation.



The general acid (hydrochloric, sulfuric, or acetic acid)-catalyzed isomerization of 2-phenylisatogen (108d) to the anthranil⁸⁰⁻⁸² 119, incorrectly assigned the oxazirane ("isoisatogen") structure 120 by early workers,^{5, 83, 84} is considered to proceed by initial addition of water across the nitron system. Isatogen ring-opening is followed by cyclization to the anthranil (see also Sections II,A,2 and III,D). However the oxirane

⁷⁷ M. J. Fowler and M. Hooper, unpublished results (1968).

⁷⁸ L. Lunazzi, G. F. Pedulli, G. Maccagnani, and A. Mangini, *J. Chem. Soc. B*, 1072 (1967).

⁷⁹ M. Bakunin and T. Vitale, *Rend. Accad. Sci. Napoli* **33**, 270 (1927) [*Brit. Chem. Abstr. A*, 328 (1929)].

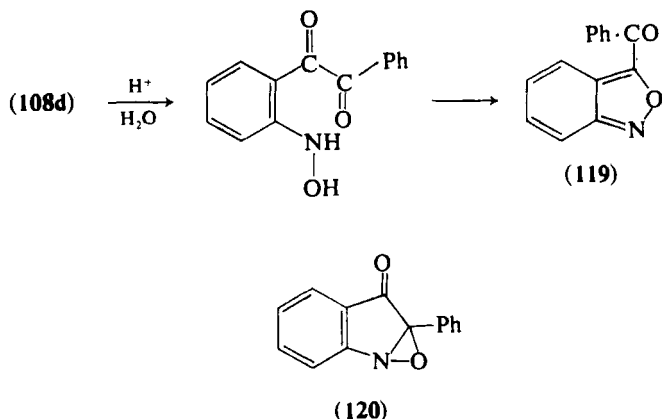
⁸⁰ J. L. Pinkus, T. Cohen, M. Sundaralingam, and G. A. Jeffrey, *Proc. Chem. Soc.*, 70 (1960).

⁸¹ M. Sundaralingam and G. A. Jeffrey, *Acta Crystallogr.* **15**, 1035 (1962).

⁸² J. L. Pinkus, G. G. Woodyard, and T. Cohen, *J. Org. Chem.* **30**, 1104 (1965).

⁸³ P. Ruggli and A. Bölliger, *Helv. Chim. Acta* **4**, 626 (1921).

⁸⁴ P. Ruggli, E. Caspar, and B. Hedegüs, *Helv. Chim. Acta* **22**, 140 (1939).

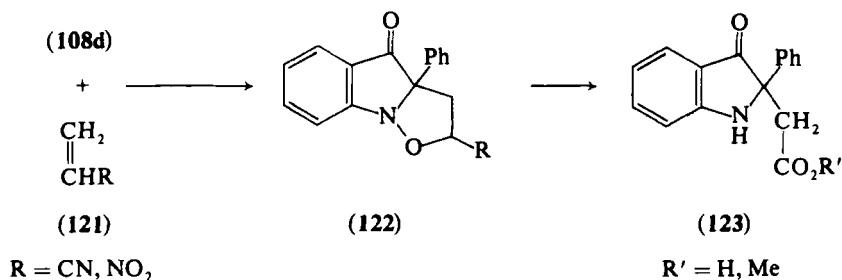


(120) is an intermediate in the photochemical isomerization of **108d** to **119**.⁸⁵

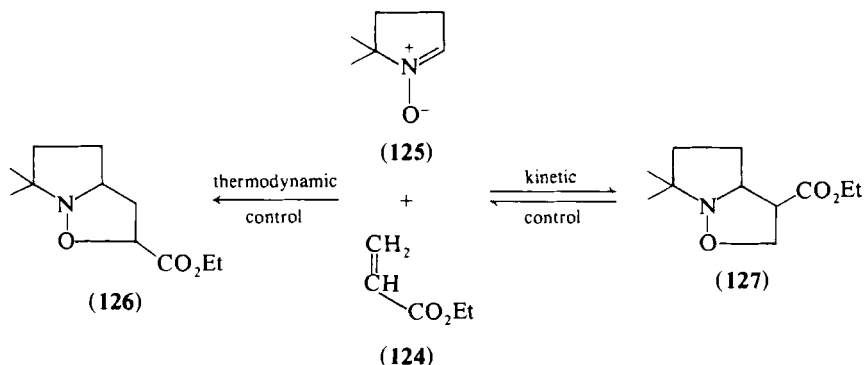
2. 1,3-Dipolar Cycloaddition Reactions

The nitron group of the isatogen ring functions as a 1,3-dipolar system and takes part in a number of cycloaddition reactions with substituted olefins and acetylenes. The resulting adducts, in most cases, are not easily isolated and undergo further reactions, particularly nucleophilic addition and/or ring expansion, to give a variety of products.

2-Phenylisatogen (**108d**) reacts with the dipolarophiles **121** regio-specifically to give isoxazolidines **122**.⁷³ The orientation of the cycloadducts is unexpected and provides an example of electron donation from oxygen, "back polarization," directing the course of a



⁸⁵ D. R. Eckroth and R. H. Squire, *J. Chem. Soc., Chem. Commun.*, 312 (1969).

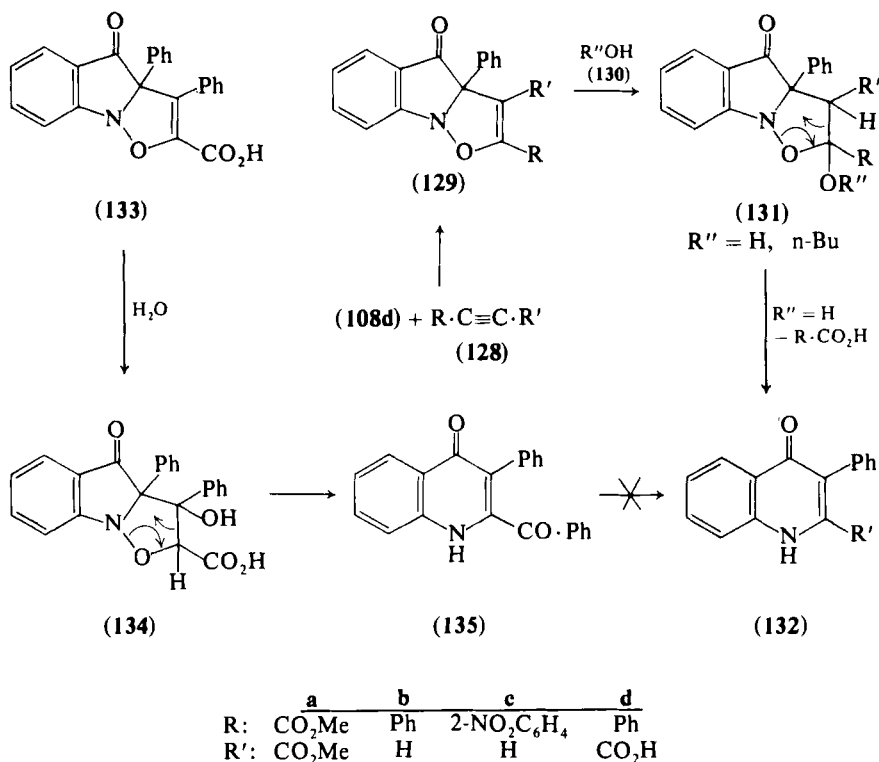


reaction of isatogens (see Section I). The isoxazolidine structures (**122**) were confirmed by their hydrolysis or methanolysis to the corresponding indolinones (**123**).⁷³ Nitrile oxides⁸⁶ and nitrones⁶ are known to participate in this type of reaction. The simple nitron **125** reacts with ethyl acrylate (**124**) to give isomeric products, which are formed as a result of a thermodynamically (**126**) or kinetically (**127**) controlled reaction.⁸⁷

The reaction of 2-phenylisatogen (**108d**) with a number of substituted acetylenes (**128**) in boiling xylene is shown in Scheme 9. Dimethyl acetylenedicarboxylate (**128a**) gives the isoxazoline (**129a**), which adds weak nucleophiles (**130**) to give isoxazolidines (**131a**). Further treatment with triethylamine in *n*-butanol results in rearrangement to the quinolone **132** ($R' = \text{CO}_2\text{Me}$).^{24, 74} Phenylacetylene (**128b**)⁷² or 2-nitrophenylacetylene (**128c**)⁷ and **108d** in boiling xylene, with⁷² or without⁷ an acid catalyst, give the quinolone **132** ($R' = \text{H}$) together with benzoic or 2-nitrobenzoic acid. Although no intermediates were isolated, the reaction can be reasonably assumed to proceed via the corresponding isoxazolines (**129**) and isoxazolidines (**131**). In contrast, the reaction of **108d** with phenylpropionic acid (**128d**) under the same conditions gives the quinolone (**135**). The formation of this compound requires the addition of water to the isoxazoline (**133**) to proceed in the reverse sense, presumably directed by the electron-withdrawing influence of the carboxyl group, to give the isoxazolidine (**134**).⁷² The possibility of **135** being an intermediate in the formation of **132** ($R' = \text{H}$) was ruled out when **135** was shown to be unaffected by treatment with acid in boiling xylene.⁷² Further studies are necessary to discover whether or not the different courses of these reactions simply reflect the different electronic properties of the acetylenes or are due to competing kinetic and thermodynamic reactions.

⁸⁶ A. Quilico, G. Stagno D'Alcontres, and P. Grünanger, *Nature (London)* **166**, 226 (1950).

⁸⁷ G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).



SCHEME 9. The reaction of 2-phenylisatogen (**108d**) with substituted acetylenes (**128**).

B. REDUCTION

The order of the ease of reduction of isatogens follows the same general pattern as that observed for nucleophilic attack at the nitron group. This is not surprising, since an electron may be considered to be the simplest example of a nucleophile. A polarographic study of the reduction of a series of isatogens (**136a–e**) shows that the redox potentials of isatogens and quinones are comparable and are influenced in the same way by substituents. Isatogens (**136a,b**) with the strongest electron-withdrawing groups in the 2-position are most easily reduced (Fig. 1). In a series of 2-aryl isatogens (**136c–e**) the redox potentials are linearly related to the Hammett value (σ_p) of the substituent in the aryl ring (Fig. 2).⁸⁸ The conclusions from the polarographic study are in

⁸⁸ J. E. Bunney and M. Hooper, *J. Chem. Soc. B*, 1239 (1970).

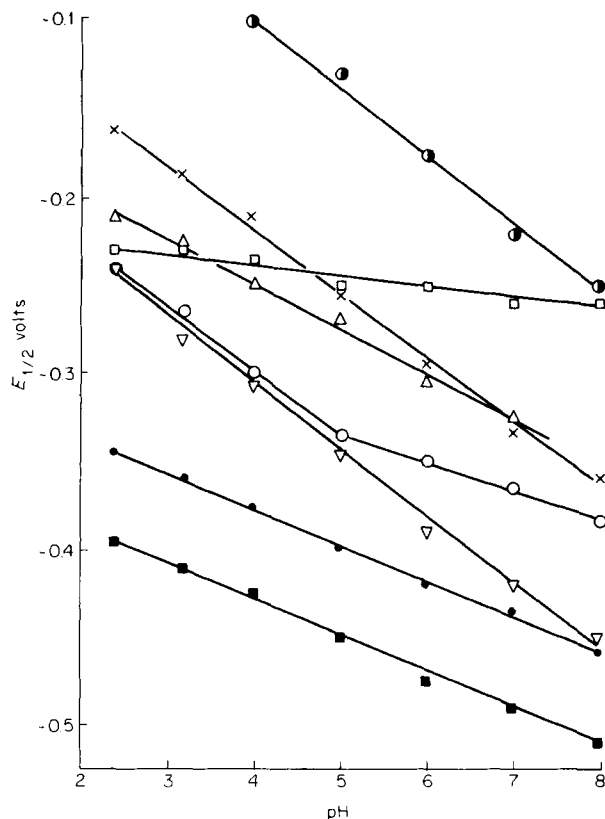


FIG. 1. Variations of the half-wave potentials of isotogens (**136a–e**) and quinones with pH. ●, 1,4-benzoquinone (1st wave); ×, **136b** (1st wave); ▽, 1,4-naphthoquinone (1st wave); ○, **136b** (2nd wave); □, **136a**; △, **136c**; ●, **136d**; ■, **136e**. Reproduced with permission from Bunney and Hooper.⁸⁸

accord with the results of the oxidation of a variety of inorganic and organic compounds by isotogens. Generally, the more reactive isotogens (**136a–c**) are the more efficient oxidizing agents, and in some cases they oxidize compounds that are unaffected by the less reactive isotogens (**136d,e**). A general scheme for the stepwise reduction of isotogens, which covers all the known reduction products, is given in Scheme 10. The number and nature of the reduction products varies with the structure of the isotogen, the nature of the reducing agent, and the stability of the reaction products (Table I).

The first step, by analogy with quinones, requires the addition of two atoms of hydrogen to give 1,3-dihydroxyindoles (**137**). All attempts to isolate or identify these compounds by chemical means have been

TABLE I
REDUCTION OF ISATOGENS^a

Reducing agent	Indolone (138) ^b	Indolone hydrate (139) ^c	Indoxyl (140) ^d	Diindoxyl (141) ^e
H ₂ /Ni ²⁹			✓	
H ₂ S ⁸⁸			✓	
SnCl ₂ /HCl ⁸²			✓	
Zn/AcOH ⁸⁹			✓	
N ₂ H ₄ ⁹⁰			✓	
NaBH ₄ ^{6,18}				✓
Fe ²⁺ ^{88,91}		✓		
HI ^{5,10,36}	✓			
POCl ₃ ⁵⁰	✓			
PhNHNH ₂ ⁶¹		✓	✓	✓
Alkyl SH/aryl SH ^{9,92}			✓	
4-NO ₂ C ₆ H ₄ SH ¹⁷	✓	✓	✓	✓
2-Naphthalenethiol ¹⁷	✓	✓	✓	✓
PhSH ¹⁸			✓	✓
Glutathione ¹⁸	✓	✓	✓	✓
Ascorbic acid ¹⁸			✓	✓
1,4-Dihydrobenzylnicotinamide ¹⁷	✓	✓	✓	✓
1,4-Dihydroxynaphthalene ¹⁷		✓		

^a Only the general class of compounds formed is indicated. For details of specific compounds consult the references.

^b Only **138d, e**.

^c Mainly **139a, b**.

^d Mainly **140a, b**.

^e Most commonly **141** (R = Ph or CO₂Me).

⁸⁹ A. Baeyer, *Ber. Deut. Chem. Ges.* **15**, 775 (1882).

⁹⁰ P. Ruggli, H. Zaeslin, and R. Grand, *Helv. Chim. Acta* **21**, 33 (1938).

⁹¹ R. M. Acheson and S. R. G. Booth, *J. Chem. Soc. C*, 30 (1968).

⁹² R. Danieli and G. Maccagnani, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 353 (1965).

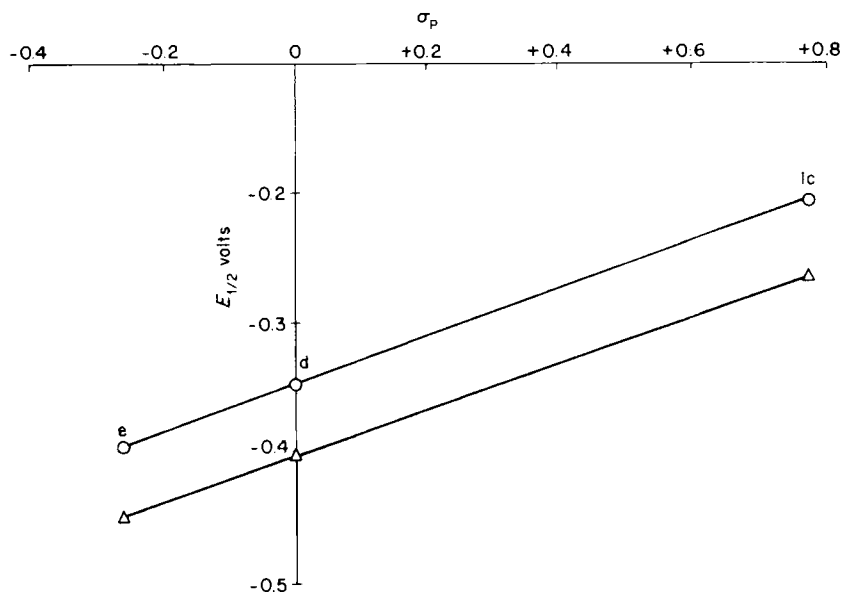
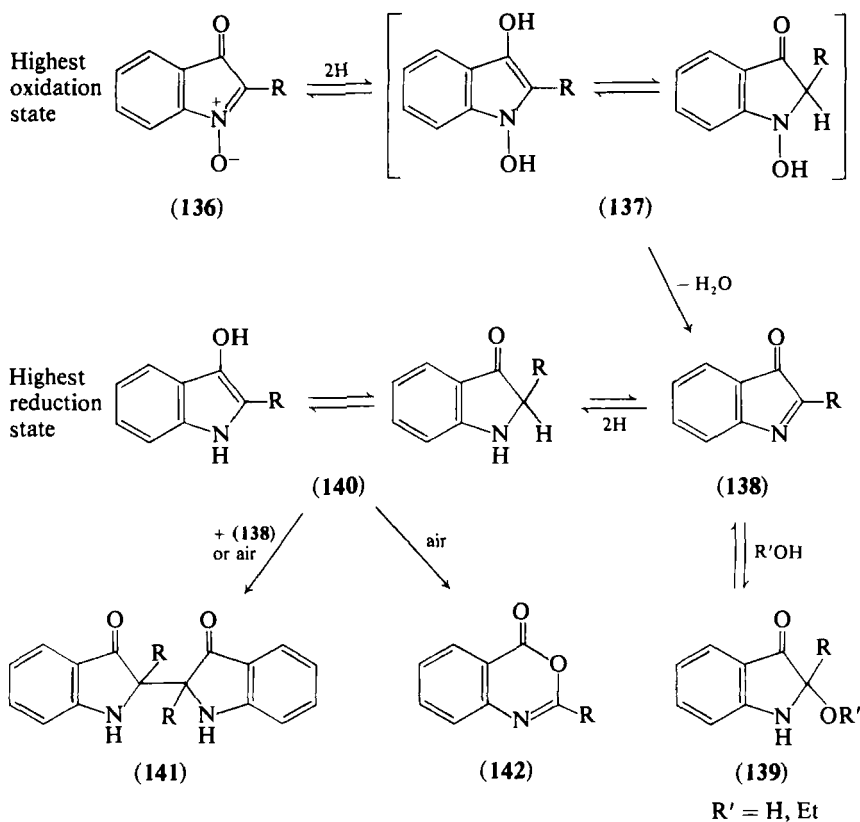


FIG. 2. Hammett σ_p values as a function of $E_{1/2}$ for isatogens (**136c–e**). O, pH 2.4; Δ , pH 5.0. Reproduced with permission from Bunney and Hooper.⁸⁸

unsuccessful. The early claim⁹³ that **136b** was reduced to **137b** with phenylhydrazine at room temperature was shown to be incorrect when the product was identified as **139b** ($R' = H$)⁶¹ (see Table I). The reaction of 6-nitro-2-phenylisatogen with acetic anhydride and sulfuric acid, reported to give the triacetate (**143**),⁵ could not be repeated by later workers¹⁷ and must be regarded as doubtful (Section III,A,1). Reduction of **136a**, by heating in toluene, xylene, or mesitylene, is reported to give a stable nitroxide radical of uncertain structure, but reduction of **136d** with ^tBuOK/DMSO gives a different radical (**144**) related to **137d**.⁵⁹ The radical (**145**) is formed from **136a** in a reversible one-electron transfer step.^{58,78} Evidence for an unstable intermediate, which is reversibly oxidized to the parent isatogen, has been obtained from the reaction of **136d** with mitochondria (Section VII). The dihydroxyindoles (**137**) would be expected to be reversibly oxidized to the parent isatogen and also readily to lose water, in an irreversible step, giving indolones (**138**). Indolones with an unsubstituted phenyl ring (**138d**), or a phenyl ring bearing an electron-releasing group, in the 2-position are sufficiently stable to be isolated. The more reactive indolones (**138a–c**) undergo nucleophilic addition, giving adducts (**139**) of varying stability (Section V,A). The reaction of **136a** with phenylhydrazine in the cold, initially

⁹³ P. Ruggli and H. Cuenin, *Helv. Chim. Acta* 27, 649 (1944).

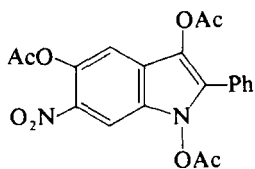


- a: R = CO₂Me
 b: R = 2-pyridyl
 c: R = 4-nitrophenyl
 d: R = phenyl
 e: R = 4-methoxyphenyl

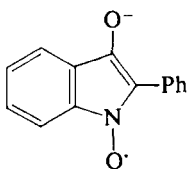
SCHEME 10

reported²⁹ to give **138a**, is now known to give the diindoxyl (**141**: R = CO₂Me).^{22,61} Indolones (**138**) are comparable with isotogens as oxidizing agents⁸⁸ and form a second theoretically reversible redox system with indoxyls (**140**). In practice, such systems are not usually reversible and a number of different products are formed.^{17,18} Indoxyls (**140a, b**) in which the enol form is stabilized by intramolecular hydrogen bonding are usually isolable, but other indoxyls are isolated only in reactions carried out in the absence of air.¹⁸ Indoxyls (**140a, b, d**) react with **138d**, in the absence of air, to give mixed diindoxyls (**141**) and are oxidized in air to symmetrical diindoxyls (e.g., **141**: R = Ph)³⁸ and

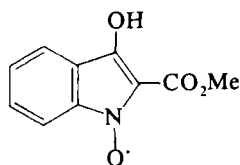
benzoxazines (**142**). The benzoxazines are unexpected products of these reduction reactions. They were identified unequivocally¹⁸ and can reasonably be assumed to be formed via peroxide and oxaziridine intermediates (see also Section III,A,1).



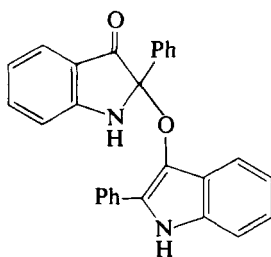
(143)



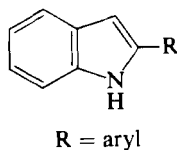
(144)



(145)



(146)



R = aryl

(147)

In contrast, the structure of the diindoxyls (**141**) is controversial. Kalb and Bayer,³ followed by Jones,²⁴ supported structure **146**. On the other hand, Hassner and Haddadin⁹⁴ and Bond,¹⁸ from a comparison of the UV spectra with those of 2,2-disubstituted indoxyls⁹⁵ have argued for **141**. Chemical evidence has also been presented in favor of **141**.¹⁸ Indolones (**138**) do not form adducts with phenols, and their water and alcohol adducts are unstable. The adducts with active methylene compounds are more stable (Section V,A). The stability of the diindoxyls corresponds to a C—C rather than a C—O linkage at the 2-position of the indolone adducts. The present evidence overwhelmingly supports **141** as the correct structure for these compounds.

Two forms of the diindoxyl (**141**; R = Ph), m.p. 180°^{3,38} and m.p. 225°^{9,53} have been mentioned in the literature. The lower melting isomer is converted into the higher melting one by heating in Dowtherm.^{17,18} The detailed structural changes are not clear, but a simple solution would be to identify one isomer as the racemic compound and the other as the meso isomer.

Early workers recognized some of the similarities between isatogens and quinones.⁵ They described 2-(2-pyridyl)isatogen as the first example of a *meta*-quinone system.⁹³ However the suggestion that methyl

⁹⁴ A. Hassner and M. J. Haddadin, *J. Org. Chem.* **28**, 224 (1963).

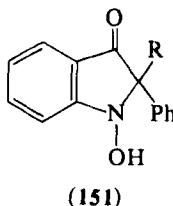
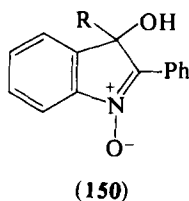
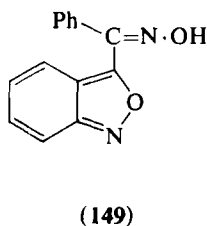
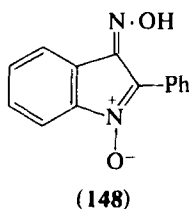
⁹⁵ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2188 (1951).

isatogenate (**136a**) and the corresponding indoxyl (**140a**) form a "quinhydrone" complex^{5,29,90} needs to be reexamined in the light of the above studies.

The reduction of 2-arylisatogens to indoles (**147**) has been achieved using thioalcohols or thiophenols in the presence of boron trifluoride.^{9,92}

C. REACTIONS AT THE CARBONYL GROUP

Nucleophilic reagents only rarely react at this group, and even then the competing reaction at the nitron group also takes place. 2-Phenylisatogen reacts with hydroxylamine in the presence of a weak acid to give a normal oxime, the "C-oxime," (**148**) and 3-benzoylanthranil oxime, the "N-oxime," (**149**)^{5,80-82} (see also **119**, Section III,A,1). The products of attack at the carbonyl group (**150**) predominate when Grignard, or organolithium, reagents react with 2-phenylisatogen.⁹⁶ Earlier it had been suggested that the minor product (**151**) was the only one formed in this type of reaction.^{5,97}



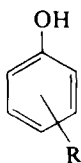
D. MISCELLANEOUS REACTIONS

2-(2-Pyridyl)isatogen is the only isatogen to react with phenols, at room temperature, forming bright red adducts. Monohydric phenols (**152a-g**) form 1:1 complexes whereas dihydric phenols (**152h-j**) and phloroglucinol (**152k**) form 1(phenol):2(isatogen) complexes. The

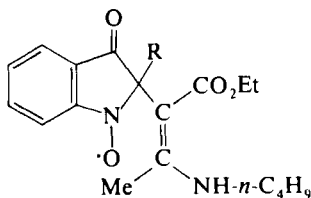
⁹⁶ C. Berti, M. Colonna, L. Greci, and L. Marchetti, *Tetrahedron* **31**, 1745 (1975).

⁹⁷ P. Ruggli, B. Hegedüs, and E. Caspar, *Helv. Chim. Acta* **22**, 411 (1939).

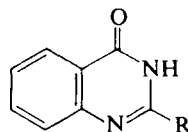
adducts are not salts but labile complexes held together by charge-transfer and hydrogen-bonding forces. Evidence has been presented indicating that the complexes consist of molecular stacks of the isatogen and the phenol¹⁷ analogous to the structure of quinhedrone.^{98,99} Similar adducts between phenols and 4-nitropyridine and its *N*-oxide have been reported.¹⁰⁰



(152)



(153)



(154)

R =

- | | |
|------------------------|------------------------|
| a: H | f: 3-CO ₂ H |
| b: 2-Me | g: 4-CO ₂ H |
| c: 4-Me | h: 2-OH |
| d: 4-Cl | i: 3-OH |
| e: 2-CO ₂ H | j: 4-OH |
| k: 3,5-di-OH | |

R = CO₂Et, 2-pyridyl

R = CO₂Me, Ph

Methyl isatogenate and 2-(2-pyridyl)isatogen react with ethyl 3-(*n*-butylamino)crotonate to give stable crystalline nitroxide radicals. The structures **153**¹⁷ have been assigned from preliminary ESR studies and by analogy with the Nenitzescu reaction involving quinones and this reagent.¹⁰¹

Methyl isatogenate and 2-phenylisatogen react with tetracyanoethylene, or trichloroacetonitrile, in boiling xylene to give quinazolones (**154**: R = CO₂Me, Ph).^{63,72} No reaction occurs with acetonitrile, and *N*-benzoylanthranilic acid is formed when 2-phenylisatogen is treated with potassium cyanide (see also Section III,A,1). No mechanism has been proposed for this unusual reaction.

IV. Synthesis of Indolones

The formation of indolones is reported to occur under a variety of conditions. In many cases the indolones themselves are not stable under the reaction conditions, particularly those involving nucleophiles or

⁹⁸ L. Michaelis and S. Grannick, *J. Am. Chem. Soc.* **88**, 1023 (1944).

⁹⁹ R. Foster and P. Hanson, *Biochim. Biophys. Acta* **112**, 482 (1966).

¹⁰⁰ F. Kröhnke and H. Schaeffer, *Chem. Ber.* **95**, 1098 (1962).

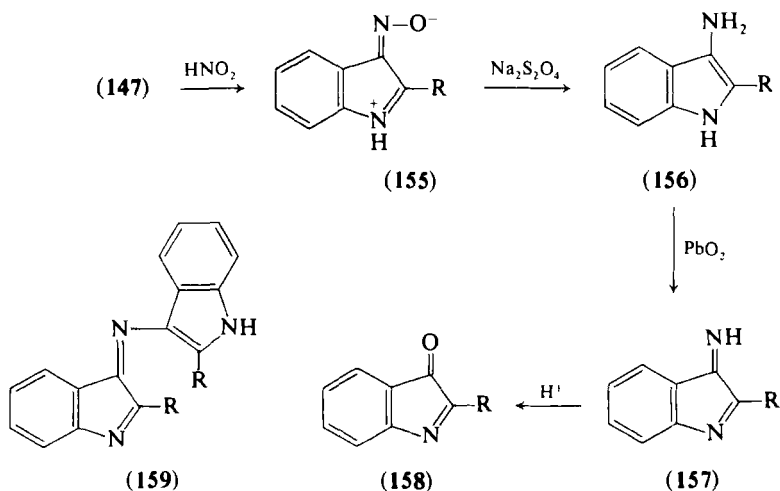
¹⁰¹ G. R. Allen, in "Organic Reactions" (W. G. Dauben, Ed. in chief), Vol. 20, p. 337. Wiley, New York, 1973.

oxidizing or reducing agents (Sections V,A,C, D, and F). It is not surprising therefore that some uncertainty surrounds the structures assigned to a number of the products of these reactions.

A. FROM 2-SUBSTITUTED INDOLES

1. The Bayer Synthesis

Bayer³ first synthesized phenylindolone (**158**; R = Ph) by the route shown in Scheme 11. This is still the best general method for the preparation of 2-arylindolones.⁴⁹ The indoles **147** are available by Fischer or Madelung syntheses. Nitrosation takes place readily to give the zwitterionic⁵⁰ indole oximes (**155**). Reduction of **155** proceeds smoothly to give the unstable 3-aminoindoles (**156**). These amines rapidly change from their original buff color to green or blue when exposed to air. One decomposition product has been identified as the dimeric compound (**159**).^{18, 102} The oxidation of **156** with lead dioxide gives the unstable imino compounds **157**, which are hydrolyzed by acid to the indolones (**158**). The yields except for the last stage are very high. The last reaction step gives higher yields when dilute, rather than concentrated, hydrochloric acid is used and when the indolone is extracted into benzene as it is formed.⁴⁹ The method is only suitable for the preparation of 2-arylindolones in which the aryl group carries electron releasing substituents, such as alkyl, alkoxy, phenyl, or weakly electron-



SCHEME 11. For all formulas, R = aryl.

¹⁰² J. Schmitt, M. Langlois, and C. Perrin, *Bull. Soc. Chim. Fr.* **4**, 1234 (1969).

withdrawing substituents, such as a chlorine atom. 2-Arylindoles with more strongly electron withdrawing substituents either fail to react or give indolone hydrates (**139**: R = 4-nitrophenyl or 2-pyridyl; R' = H). All attempts to prepare 2-alkylindolones by this route failed.⁴⁹

2. Oxidation with Monoperphthalic Acid (MPA)

The recently reported⁴⁸ oxidation of 2-substituted indoles (**147**: R = alkyl, 2-pyridyl, CO₂Et) with MPA gives, in variable amounts, indolones, indolone hydrates, diindoxyls, and benzoxazines. The reactions proceed via the intermediate indoxyls as set out in Scheme 10 (Section III,B; cf. Sections II,B,1; V,D). This synthetic route makes available for the first time 2-alkylindolones (**158**: R = alkyl). These compounds, with the exception of 2-*t*-butylindolone, are too reactive to be isolated except as their hydrates (**139**: R = alkyl; R' = H). The stability of **158** (R = *t*-butyl) is due to the large *t*-butyl group hindering nucleophilic attack at the 2-position⁴⁸ (Section V,A) and the absence of hydrogen atoms on the α -carbon atom, which prevents isomerization to the preferred 2-methyleneindolinone structure (Sections I and II, A,4).^{4,36} Other workers^{103,104} obtained only diindoxyls (**141**: R = alkyl) when 2-alkylindoles (**147**: R = alkyl) were oxidized by dilute peracetic acid.

3. From Isatin α -Chloride

"Isatin α -chloride" (2-chloroindolone, **160a**) has been known for a long time.¹⁰⁵ It is usually considered as a derivative of isatin,¹⁰⁶ from which it is prepared by treatment with phosphorus pentachloride in boiling benzene. The methyl ether (**160b**) is readily prepared from the silver salt of isatin.¹⁰⁷

The reaction of isatin α -chloride (**160a**) with electron-rich aryl compounds, in the presence of a Lewis acid, gives indolone salts (**161**) from which the indolones (**162**) can be liberated on treatment with base.^{49, 108, 109} The reaction of **160a** with various amines, under these conditions, has been reported¹⁰⁸ to give the unstable indolones (**163**) although later attempts to repeat the synthesis were unsuccessful.⁴⁹

¹⁰³ F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.* **93**, 1373 (1963).

¹⁰⁴ F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.* **93**, 1382 (1963).

¹⁰⁵ A. Baeyer, *Ber. Deut. Chem. Ges.* **12**, 456 (1879).

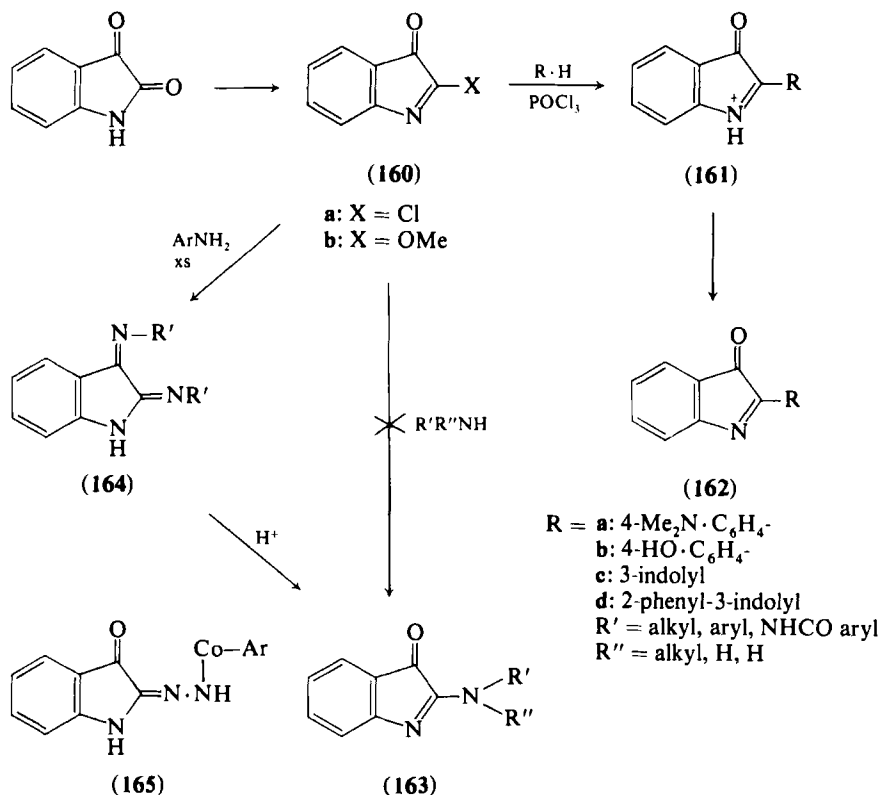
¹⁰⁶ W. C. Sumpter and F. Müller, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. VIII, chapter 3. Wiley (Interscience), New York, 1954.

¹⁰⁷ A. Baeyer and S. Oekonomides, *Ber. Deut. Chem. Ges.* **15**, 2093 (1882).

¹⁰⁸ J. van Alphen, *Rec. Trav. Chim.* **60**, 138 (1941).

¹⁰⁹ T. E. Young and D. S. Auld, *J. Org. Chem.* **28**, 418 (1963).

The piperidino compound (**163**: $R', R'' = -(CH_2)_5-$) is easily hydrolyzed,¹¹⁰ and the anilino compound (**163**: $R' = Ph$; $R'' = H$) cannot be prepared by this route.¹¹¹ A number of these compounds have been prepared by the alternative route **160a** \rightarrow **164** \rightarrow **163**.¹¹² The reaction conditions were modified in more recent studies.¹¹³ Robertson⁸ identified **163** ($R' = 2$ -pyridyl; $R'' = H$) as the unexpected product of the reaction between 2-nitrophenylpropionic acid and 2-aminopyridine. Further studies are needed to clarify these conflicting, and in some cases tentative, reports. The tautomerism of these compounds (**163**: $R' = \text{aryl}$; $R'' = H$) is worthy of further study¹¹¹ (cf. Section II,A,4). Recently, a study of the tautomerism of the carbazide derivatives (**165**) has been made; both tautomers (**163**, **165**) were reportedly identified.¹¹⁴



¹¹⁰ T. Hino, M. Nakagawa, and T. Hashizume, *Tetrahedron Lett.*, 2205 (1970).

¹¹¹ R. K. Callow and E. Hope, *J. Chem. Soc.*, 1194 (1929).

¹¹² J. Grimshaw and W. G. Begley, *Synthesis*, 496 (1974).

¹¹³ C. K. H. Chu, J. Patel, and M. Hooper, unpublished results (1975).

¹¹⁴ A. B. Tomchen, V. S. Dmitrukha, T. N. Timofeeva, and P. S. Peikis, *Zh. Org. Khim.* **10**, 1519 (1974) [*CA* **81**, 168944 (1974)].

There was no reaction between the sodium salts of active methine compounds and **160**⁴⁹ (cf. Section II,A,4).

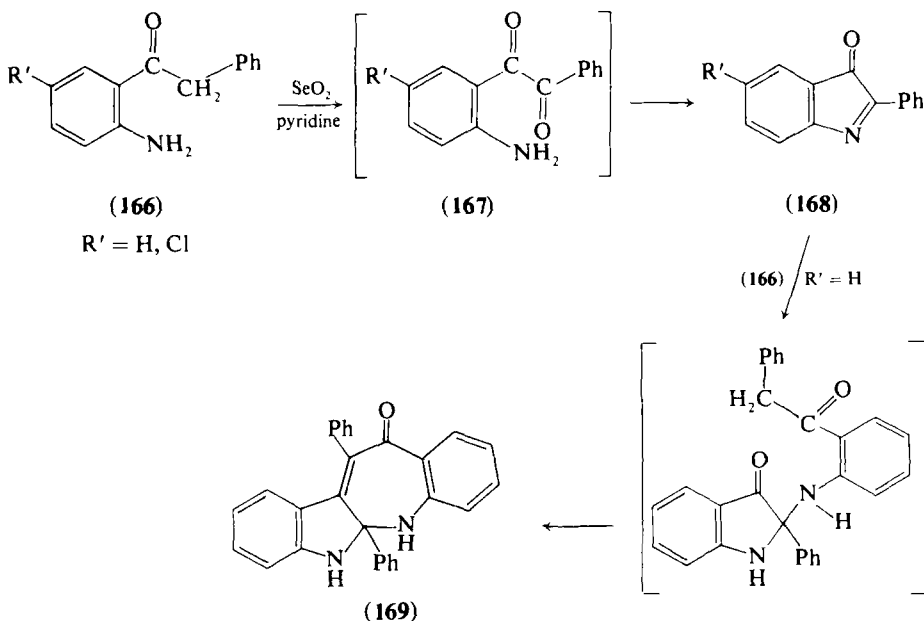
4. From Miscellaneous Compounds

Indoxyls (**140**) have been reported to be oxidized under a variety of conditions to indolones (**158**). However, the literature claims are conflicting. Ruggli²⁹ claimed to oxidize 2-phenyl-6-nitroindoxyl to the corresponding indolone with nitrous acid, but attempts to repeat this reaction failed.²² Benzoyl peroxide oxidized 2-(4-aminophenyl)-4,6-dinitroindoxyl to the corresponding indolone,²⁰ but methyl indoxyl-2-carboxylate to the diindoxyl (**141**; $R = CO_2Me$).²² Isatogens are reduced under a variety of conditions to a number of different products which include some indolones (**158**; $R = Ph$, 4-methoxyphenyl) and indolone hydrates (**139**; $R = CO_2Me$, 2-pyridyl; $R' = H$); for a detailed discussion see Section III,B and Table I.

B. INTRAMOLECULAR CYCLIZATIONS

1. Oxidation of 2-Aminophenyl Benzyl Ketones

Selenium dioxide oxidation of the ketones (**166**; $R' = H, Cl$) is reported¹¹⁵ to give the corresponding indolones (**168**) in moderate yield

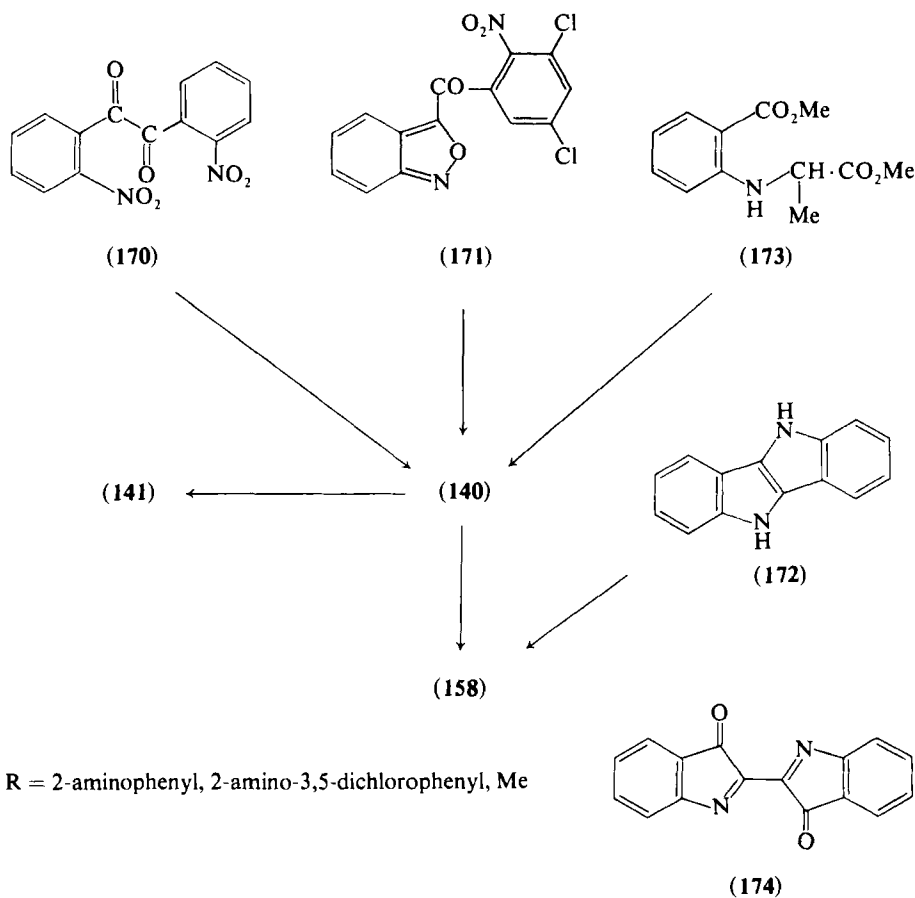


¹¹⁵ J. Schmitt, C. Perrin, M. Langlois, and M. Suquet, *Bull. Soc. Chim. Fr.* **4**, 1227 (1969).

via the intermediate benzils (**167**). However, when the reactions were repeated only traces of the indolone (**168**; $R' = H$) were detected. The major product was assigned the indolobenzazepine structure (**169**), which was synthesized from 2-phenylindolone and **166** ($R' = H$) in the absence of selenium dioxide.⁴⁹ The reaction is thought to involve nucleophilic addition of the ketone (**166**; $R' = H$) to the indolone (**168**; $R' = H$) followed by cyclization (Sections V,A,1 and 2).

2. Miscellaneous Reactions

Reduction of the benzil (**170**) and the anthranil (**171**) (original structure assigned incorrectly; see Section III,A,1) has been reported to give the corresponding indolones (**158**; $R = 2\text{-aminophenyl}$, 2-amino-



SCHEME 12

3,5-dichlorophenyl)^{115a} The reactions involve reduction followed by treatment of the products with air in the presence of ammonia. It now seems probable that the reactions proceed via the indoxyls (**140**), which are oxidized under these conditions to diindoxyls (**141**), see also (Sections III,B; IV,A,2 and 4). The indolone structure has also been assigned to the product of chloramine oxidation of the indoloindole (**172**);¹¹⁶ it has a different melting point from the compound to which Ruggli assigned the same structure. The cyclization of the phenylglycines (**173**) with sodium methoxide in the presence of air, at first thought to give 2-methylindolone,¹¹⁷ has now been shown to give the diindoxyl **141** (R = Me) via the indoxyl intermediate **140**.^{94, 118} Diindolone (dehydroindigo, **174**) is obtained when indigo is oxidized by chlorine or by lead dioxide.¹¹⁹ All these reactions are summarized in Scheme 12.

V. Chemical Properties of Indolones

Indolones have both an azomethine and carbonyl group carbon atom within the same five-membered ring system. The azomethine group is the more reactive center and readily takes part in reactions typical of that group.¹²⁰

A. NUCLEOPHILIC ADDITION TO THE AZOMETHINE GROUP

Simple weak nucleophiles readily add across the azomethine linkage to give adducts (**175**) of varying stability. In contrast to the deeply colored indolones the adducts are usually yellow-green solids that give strongly fluorescent solutions. The extent of reaction and the stability of the adducts varies with the structure of the indolone and the nature of the nucleophile. The indolones may usefully be subdivided into three groups; compounds in which the 2-substituent extends the conjugation of the azomethine group through an unsaturated carbon atom (**158**: R = aryl, CO₂R), compounds in which the 2-substituent is linked through a saturated carbon atom (**158**: R = alkyl), and compounds with a heteroatom attached to the 2-position (**160**, **163**). 2-Phenylindolone

^{115a} P. Ruggli and H. Zaeslin, *Helv. Chim. Acta* **18**, 845 (1935).

¹¹⁶ H. Paul and A. Weise, *Z. Chem.* **4**, 147 (1964).

¹¹⁷ O. Neunhoffer and G. Lehmann, *Chem. Ber.* **94**, 2960 (1961).

¹¹⁸ E. Giovannini, F. Farkas, and J. Rosales, *Helv. Chim. Acta* **46**, 1326 (1963).

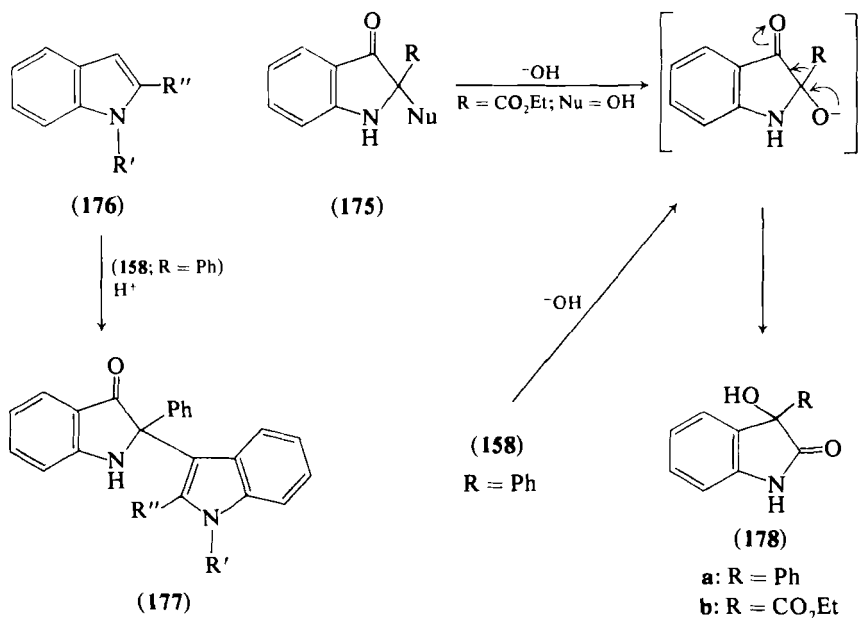
¹¹⁹ W. C. Sumpter and F. W. Miller, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. VIII, Chapter 7. Wiley (Interscience), New York, 1954.

¹²⁰ S. Patai, ed., "The Chemistry of the Carbon-Nitrogen Double Bond." Wiley (Interscience), New York, 1970.

(**158**: R = Ph) is the most widely investigated of these compounds and serves as a suitable reference compound. Kalb and Bayer³ reported the methanol, ammonia, aniline, and sodium bisulfite adducts of this compound. The reactivity of the indolone increases when the electron density at the 2-position is reduced. In these cases (**158**: R = 4-nitrophenyl, 2-pyridyl, CO₂alkyl),^{49, 61, 62, 91} the indolone adducts (**175**: Nu = OH, OEt) are stable and isolable; the free indolones do not exist. The 2-alkylindolones (**158**: R = alkyl), in which the conjugation of the azomethine group is less extensive, are also very reactive. They too are only isolated as adducts (**175**: R = alkyl; Nu = OH) with the exception of **158** (R = *t*-Bu, Section IV,A,2).

2-Alkylthioindolones are known only as their adducts (**175**: R = SME; Nu = SMe).¹²¹ Adducts from indolones with nitrogen, oxygen, or chlorine attached to the 2-position are too unstable to be isolated; such indolones are rapidly hydrolyzed in moist air to isatin.^{106, 110, 112}

Ch'ng⁴⁹ has investigated the reactions of 2-phenylindolone (**158**: R = Ph) with a variety of nucleophiles which may conveniently be classified according to the nature of the atom forming the bond at the 2-position (**175**). The stability of the adducts increases along the series O < N < C. The ethanol, ammonia, and amine adducts (**175**: R = Ph; Nu = OH, OEt, NH₂, NEt₂, NHPH) break down readily, especially in polar



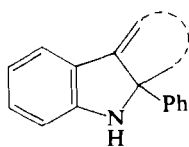
¹²¹ J. T. Baker and C. C. Duke, *Aust. J. Chem.* **25**, 2467 (1972).

solvents. The adducts with active methylene compounds, such as malonic esters and their derivatives, are stable in most solvents but slowly decompose in acetic acid and when heated at their melting points (see also Section III,B). Diindolone (**174**) forms bis-adducts with sodium bisulfite and acetic acid.¹¹⁹ In the presence of acid catalysts, which enhance the reactivity of the azomethine group, 2-phenylindolone reacts with a number of substituted indoles (**176**), at the electron-rich 3-position, to form bis-indolyl compounds (**177**).¹²²

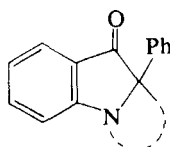
2-Phenylindolone with hydroxide ion gives the dioxindole (**178a**).³ A similar product (**178b**) is formed when the adduct **175** ($R = CO_2Et$; $Nu = OH$) is treated with hydroxide ion. In this case, the rearrangement involves a 1,2-shift of the ester grouping,⁹¹ not a ring-opening process.³ It is reasonable to assume that both reactions proceed by a common mechanism.

B. RING FUSION REACTIONS

Ring fusion can take place across the 2,3- (**179**) or 1,2- (**180**) positions of the indole ring in 2-phenylindolone. Usually stable products are formed, but in a few cases intramolecular rearrangement reactions occur.



(179)



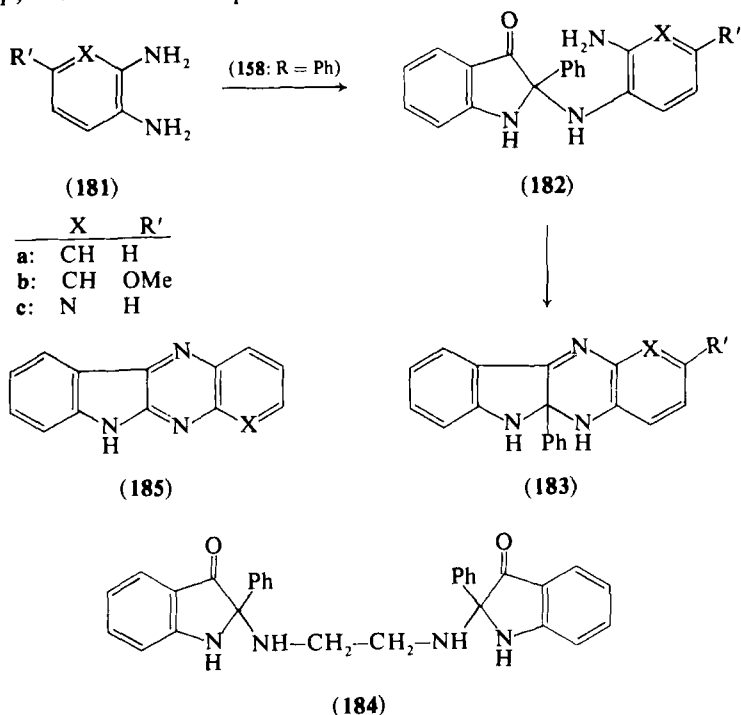
(180)

1. Ring Fusion across the 2,3-Position

2-Phenylindolone (**158**; $R = Ph$) reacts with aromatic 1,2-diamines (**181a-c**) to form indoloquinoxalines (**183**). The reaction proceeds by initial nucleophilic addition to the more reactive azomethine group (**182**) followed by cyclization through the carbonyl group. Ethylenediamine, a more flexible molecule, fails to form an indoloquinoxaline but gives only the bis adduct **184**.⁴⁹ The structure of the quinoxalines arising from the reactions with the unsymmetrical diamines (**181b,c**) were assigned on the assumption that the more strongly basic amino group first attacks the azomethine group. The analogous fully aromatic compounds (**185**; $X = CH$ or N) derived from isatin have been shown to arise by attack of

¹²² M. Colonna, L. Greci, and L. Marchetti, *Gazz. Chim. Ital.* **105**, 985 (1975).

the more strongly basic amino group at the more reactive carbonyl group, in this case the 3-position.^{123,124}



Seven-membered rings can also be formed across the 2,3-position by bifunctional nucleophiles having an amino and an active methylene group (**169**: Section IV,B,1).

2. Ring Formation across the 1,2-Position

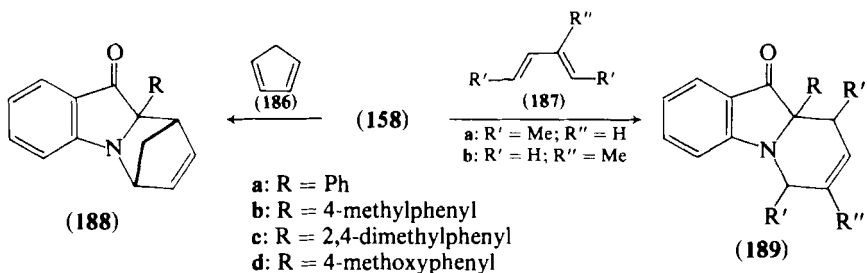
a. *Addition of Dienes.* The 2-arylindolones (**158**) react with the dienes **186** and **187**, in the presence of aluminum trichloride or perchloric acid, to form the cycloadducts **188** and **189**. The stereochemistry of **189** (R = Ph; R' = H; R'' = Me) was argued on theoretical grounds. Other less reactive dienes, such as butadienes, furan, and anthracene, did not react.¹²⁵ These reactions provide a rare example of the reluctant participation of the azomethine linkage in Diels-Alder reactions.¹²⁶

¹²³ F. D. Popp, *J. Heterocycl. Chem.* **6**, 125 (1969).

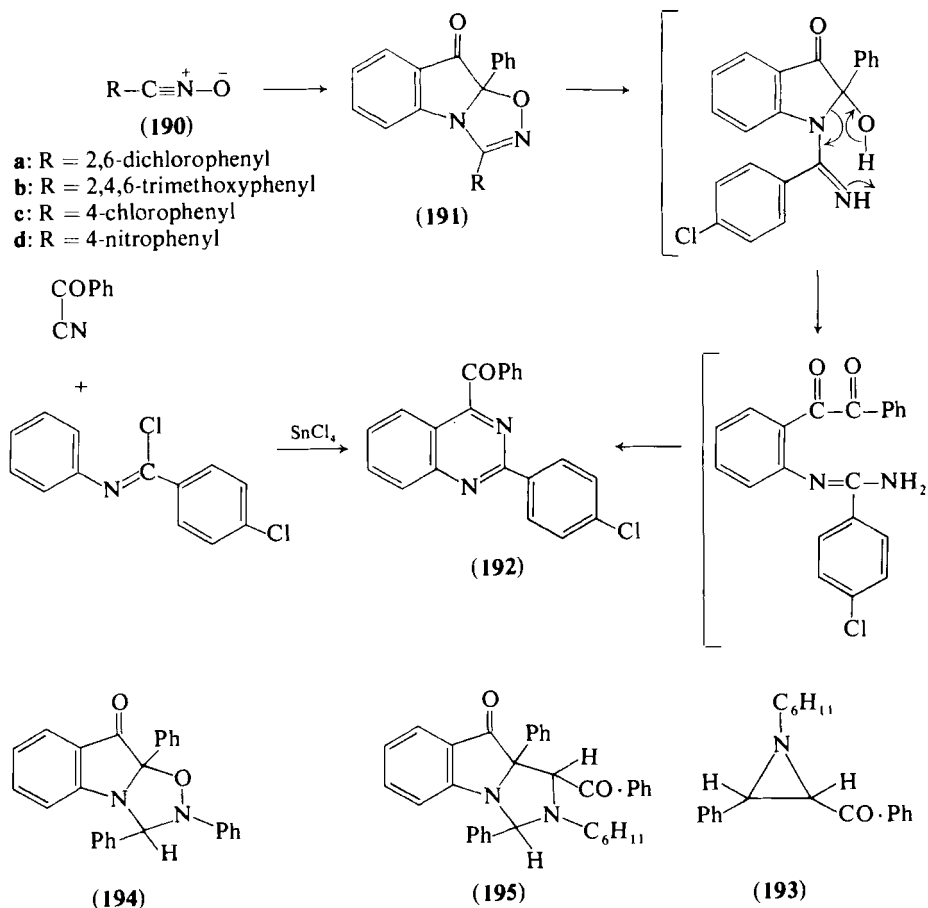
¹²⁴ M. Seth, A. P. Bhaduri, N. M. Khanna, and M. L. Dhar, *Ind. J. Chem.* **12**, 124 (1974).

¹²⁵ H. S. Ch'ng and M. Hooper, *Tetrahedron Lett.*, 1527 (1969).

¹²⁶ J. Hamer, ed., "1,4-Cycloaddition Reactions. The Diels-Alder Reaction in Heterocyclic Synthesis," p. 128. Academic Press, New York, 1967.



b. *1,3-Dipolar Cycloadditions.* The reactions of benzonitrile oxides with azomethine compounds are well documented and have been shown to give 1,3,4-oxadiazoles.¹²⁷ 2-Phenylindolone (158: R = Ph) reacts with

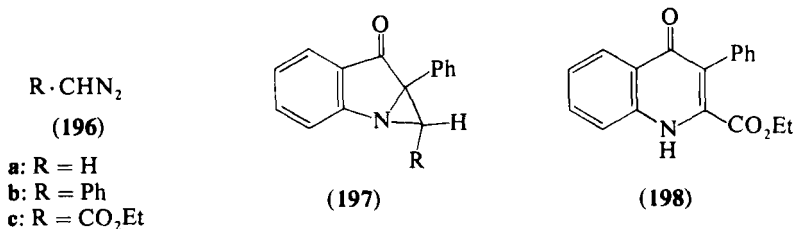


¹²⁷ T. Mukayama and T. Hoshino, *J. Am. Chem. Soc.* **82**, 5339 (1950).

the nitrile oxides **190a-d**¹²⁸⁻¹³⁰ to give the corresponding oxadiazoles (**191a-d**).⁴⁹ The structure of **191c** was confirmed by catalytic hydrogenation, which gave the quinazoline **192**. Hydrogenolysis of the N—O bond,¹³¹ analogous to that proposed earlier⁸⁰⁻⁸² (see also **171** → **140**; Section IV,B,2) is followed by ring opening and an alternative intramolecular cyclization to the quinazoline. The structure of **192** was confirmed by an independent synthesis.^{132,133}

2-Phenylindolone (**158**; R = Ph) also reacts with other 1,3-dipolar molecules. *N*- α -Diphenylnitrone¹⁴ and *cis*- and *trans*-aziridines **193**^{134,135} form the expected adducts (**194**, **195**).⁴⁹ The stereochemistry of **195** has not yet been elucidated. 2-Phenylisatogen does not react with 2-phenylindolone; under these conditions the starting materials were recovered.⁴⁹

c. Miscellaneous Reactions. Aziridines (**197**) are formed when 2-phenylindolone (**158**; R = Ph) reacts with diazo compounds in the dark (**196a,b**) or on irradiation (**196c**). In the latter case the ring-expanded quinoline **198** is also formed.⁴⁹



C. REDUCTION

The reduction of indolones is described together with the reduction of isatogens. The major products of reduction are indoxyls and diindoxyls. In some cases the indoxyls are oxidized by air to benzoxazines (Section III,B). Indolones are comparable with isatogens as oxidizing agents⁸⁸

¹²⁸ C. Grundmann and J. M. Dean, *J. Org. Chem.* **30**, 2809 (1965).

¹²⁹ J. T. Hackmann and P. A. Harthoorn, Brit. Patent 949,371 (1964) [*CA* **60**, 11949 (1964)].

¹³⁰ G. Grundmann and G. F. Kite, *Synthesis*, 156 (1973).

¹³¹ N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocycl. Chem.* **2**, 418 (1963).

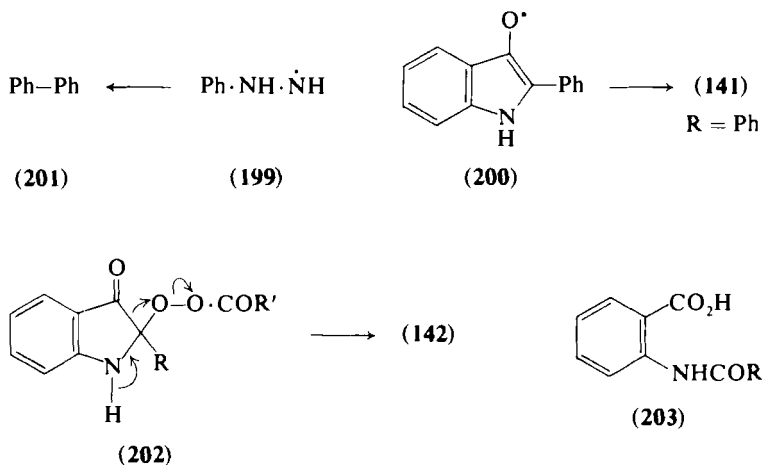
¹³² W. L. F. Armarego in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 24: "Quinazolines", Part 1 of "Fused Pyrimidines" (D. J. Brown, ed.), Chapter 3, p. 42. Wiley (Interscience), New York, 1967.

¹³³ H. E. Foster and M. Hooper, unpublished results (1975).

¹³⁴ J. W. Lown, J. P. Moses, and R. Westwood, *Can. J. Chem.* **47**, 4335 (1969).

¹³⁵ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **48**, 2215 (1970).

and function as hydrogen acceptors in a number of reactions. 2-Phenylindolone (**158**: R = Ph) reacts with phenylhydrazine to give biphenyl (**201**) and the diindoxyl (**141**: R = Ph) via the intermediate free radicals (**199** and **200**).¹³⁶ Diindolone (**174**) is reduced to indigo by hydriodic acid and hydroquinone.¹¹⁹



D. OXIDATION

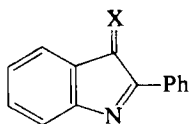
Indolones (**158**: R = aryl) or their water adducts (**175**: R = aryl, alkyl; Nu = OH) are oxidized by peracids, under mild conditions, to benzoxazines (**142**: R = aryl, alkyl). The reaction is a general one. The reaction may proceed by the intermediate oxirane (**120**) or by initial addition of the peracid across the azomethine linkage (**202**).⁴⁸ Oxidation by aqueous permanganate or dichromate gives *N*-acylantranilic acids (**203**: R = aryl, alkyl).⁴⁸⁻⁵⁰

E. REACTIONS AT THE CARBONYL GROUP

The carbonyl group of 2-phenylindolone (**158**: R = Ph) reacts to give the oxime,^{22, 137} 2,4-dinitrophenylhydrazone, and semicarbazone (**204**).⁴⁹ With phenylmagnesium bromide it gives a compound identified as the indolenine (**205**).⁴⁹ In this reaction the reactivity of the carbonyl group resembles that in isatogens (Section III,C).

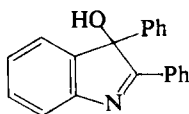
¹³⁶ M. Colonna and L. Greci, *Gazz. Chim. Ital.* **99**, 940 (1969).

¹³⁷ N. Campbell and R. C. Cooper, *J. Chem. Soc.*, 1208 (1935).

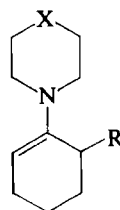


(204)

X = N·OH, N·NHCONH₂,
N·NH-2,4-(NO₂)₂C₆H₃

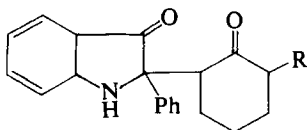


(205)

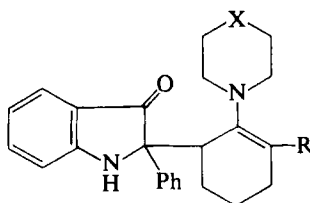


(206)

X = O, CH₂
R = H, Me



(208)



(207)

F. MISCELLANEOUS REACTIONS

2-Phenylindolone (**158**; R = Ph) reacts with enamines (**206**) to form adducts (**207**); the reaction is reversible. The adducts are readily hydrolyzed to the corresponding carbonyl compounds (**208**).¹³⁸

VI. The Spectroscopic Properties of Isatogens and Indolones

No detailed spectroscopic studies have yet been carried out on these compounds, but useful data have accumulated in the course of investigations into their syntheses and chemical reactions.

A. ULTRAVIOLET SPECTRA

The principal absorption band of 2-arylisatogens (**209**) occurs around 280 nm, log ϵ 4.2–4.6. The band is usually broad and often shows more than one maximum (Table II). It is sensitive to substituents in the 2-position of the aryl ring, being progressively displaced to lower wavelengths as the size of the substituent increases and coplanarity of the two ring systems is lost; λ for **209a** > **b** > **c** > **d**.¹⁸ In ethanol solution the 270 nm band in **209b** slowly decreases in intensity and a

¹³⁸ C. Berti, L. Greci, and L. Marchetti, *Gazz. Chim. Ital.* **105**, 993 (1975).

new band, associated with the ψ -indoxyl structure¹³⁹ of the adduct (210) appears at 235 nm⁶⁶ (Sections III,A,1 and III,B).

2-Phenylindolone (158: R = Ph) shows a similar shift when nucleophilic addition occurs at the azomethine group (175).¹⁴⁰ The reported spectra⁵⁰ of 158 (R = Ph) and the adducts (175: R = Ph; Nu = OH, OEt) in carbon tetrachloride are very similar, indicating dissociation of the adducts in this solvent (Section V,A,1). 2-(2-Pyridyl)-indolone hydrate (175: R = 2-pyridyl; Nu = OEt) fluoresces strongly at 530 nm (λ_{ex} 400 nm).⁸

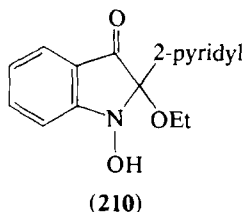
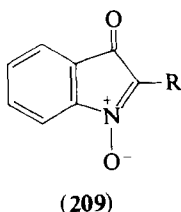


TABLE II
PRINCIPAL ULTRAVIOLET ABSORPTION BANDS OF ISATOGENS¹⁸ AND INDOLONES^{49,50}

Compound	λ_{max} nm (log ϵ)	Solvent
(209): R =		
a: Ph	279 (4.60), 286 (4.60)	EtOH
b: 2-Pyridyl	270 (4.48)	EtOH
c: 2-Methoxyphenyl	253 (4.25), 265 (3.47), 279 (4.39)	EtOH
d: 2-Nitrophenyl	257.5 (4.43)	EtOH
e: 4-Methoxyphenyl	289 (4.47), 296 (4.46)	EtOH
f: 4-Nitrophenyl	293 (4.31)	EtOH
158: R = Ph	262 (4.40) 250 (4.57), 265 (4.70)	C ₆ H ₁₂ CCl ₄ ⁵⁰
175: R = Ph; Nu = OH, OEt, CH(CO ₂ Et) ₂	231-235 (4.2-4.6)	EtOH

B. INFRARED SPECTRA

The outstanding feature of these spectra is the strong carbonyl absorption, 1700-1720 cm⁻¹ (isatogens) and 1710-1715 cm⁻¹ (indolones), which are typical of conjugated carbonyl groups in five-

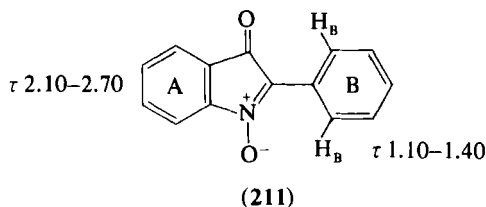
¹³⁹ A. I. Scott "Interpretation of the Ultraviolet Spectra of Natural Products," p. 175. Pergamon, Oxford, 1964.

¹⁴⁰ M. Hooper, unpublished results (1973).

membered ring compounds.¹⁴¹ A band at 1175 cm^{-1} in spectra of isotogens has been assigned to the N^+-O^- stretching vibration.⁷

C. NMR SPECTRA

The spectra of isotogens are characterized by the almost equivalent values for all four protons in ring A (211), the carbonyl and nitron groups having similar effects. These same groups deshield the two ortho protons H_B of ring B, which appear at the lowest field. Structural assignments have been made using these values.⁷ In 2-arylindolones the four protons in ring A form broad multiplets showing that the carbonyl and azomethine groups do not have the very similar effects seen with the carbonyl and nitron groups in isotogens. The two ortho protons corresponding to H_B occur at low field, τ 1.6–2.1, being deshielded by the adjacent carbonyl and azomethine groups.^{49,50}



D. MASS SPECTRA

Indolones show a very simple fragmentation pattern on electron impact. The most abundant ion is usually the molecular ion followed by the $(\text{M}-\text{CO})^+$ and $(\text{M}-\text{CHO})^+$ ions (Table III). 2-Phenylindolone (Fig. 3) is used to illustrate the general fragmentation pathways (Scheme 13, Fig. 3). Pathway *a* predominates; metastable transitions are associated with loss of CO and HCN. Loss of small molecules from tricyclic ions analogous to the phenanthridine ion are well known.^{142,143} Doubly charged ions at m/e 103.5 and 89.5 correspond to the major ions in the spectrum M^{2+} and $(\text{M}-\text{CO})^{2+}$. Pathway *b* becomes of increased significance when the aryl ring carries strongly electron-releasing groups in the 4-position (Table III). Cleavage *c* is an alternative very minor pathway giving rise to ions of ~2% abundance.⁴⁹

¹⁴¹ L. J. Bellamy "The Infrared Spectra of Complex Molecules," 3rd ed., Vol. 1, p. 168. Chapman & Hall, London, 1975.

¹⁴² T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, 206 (1965).

¹⁴³ D. R. Eckroth, *Chem. Commun.*, 465 (1970).

TABLE III
FRAGMENTATION OF 2-ARYLINDOLONES ON ELECTRON IMPACT⁴⁹

R=	% Ion abundance				
	M ⁺	Pathway <i>a</i>		Pathway <i>b</i>	
		(M-CO) ⁺	(M-CHO) ⁺	(M-R·CN) ⁺	(M-C ₆ H ₄ CO) ⁺
Phenyl	100	100	56	10	10
4-Methylphenyl	50	100	27	9	4
2,4-Dimethyl-phenyl	100	80	24	3	11
4-Methoxyphenyl	100	93	5	25	7
4-Dimethylamino-phenyl	100	89	33	26	3

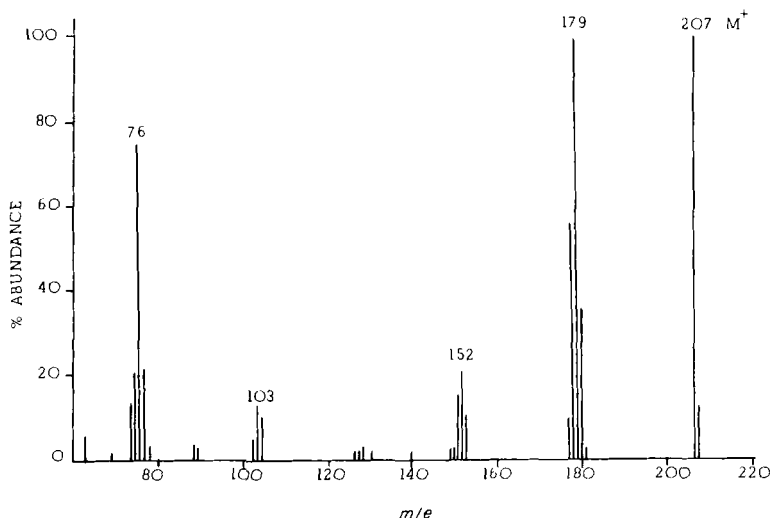
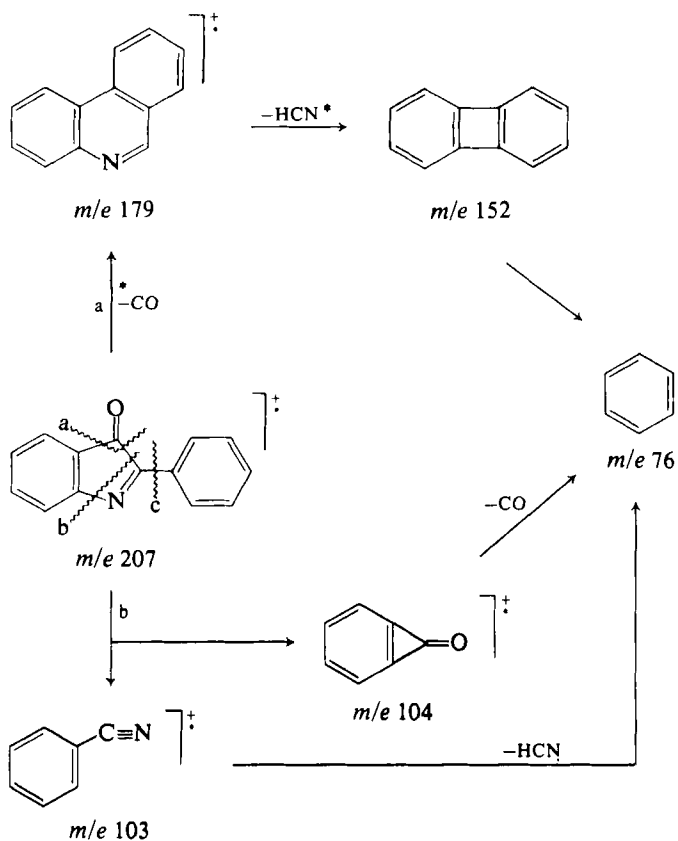


FIG. 3. Mass spectrum of 2-phenylindolone.

On electron impact, 2-arylisatogens give rise to a greater variety of fragment ions (Table IV). The major peaks correspond to the molecular ion and (M-OH)⁺. The (M-O)⁺ peak common in *N*-oxides¹⁴² is not so abundant. Metastable transitions associated with both losses have been reported.^{18, 143} The preferred loss of OH requires abstraction of a hydrogen atom, presumably from the ortho position of the 2-aryl ring, by an intramolecular process (Scheme 14). Where this is not possible (Table IV, R = CO₂Me) the (M-O)⁺ ion only is observed. In contrast to the 2-arylindolones, (M-CO)⁺ and (M-CHO)⁺ ions occur only in very



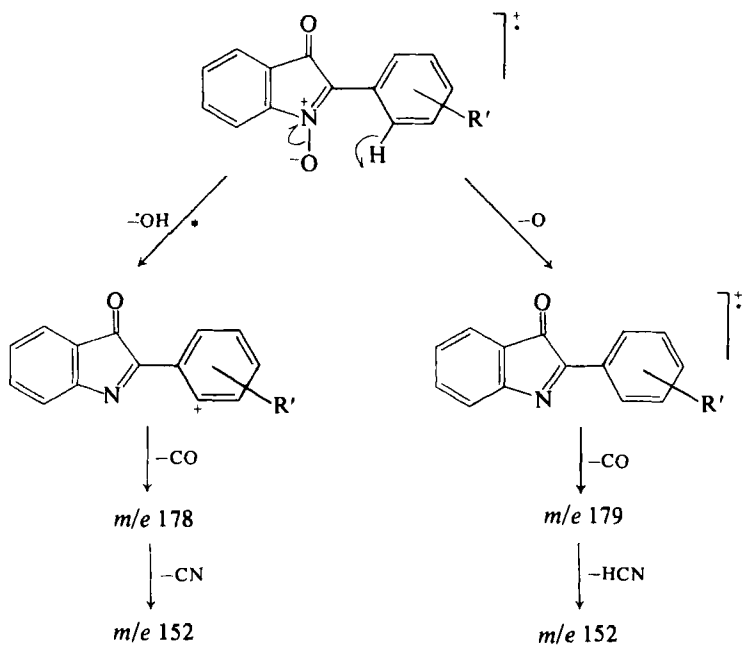
SCHEME 13

low abundances. Decomposition of the $(M-O)^+$ and $(M-OH)^+$ ions might be expected to proceed by one of the processes observed for 2-phenylindolone (Scheme 13). However, the abundance of ions corresponding to sequential loss of CO ($M-OH-CO$) and CN ($M-OH-CO-CN$) (Scheme 14) is small. This is clearly seen by comparing the mass spectrum of 2-phenylisatogen (Fig. 4) with that of the indolone (Fig. 3). The ions $(M-CO_2)^+$, $(M-2CO)^+$ and RCO^+ are indicative of fragmentation processes involving extensive rearrangement of the isatogen via an oxirane.¹⁴³ The $(M-CO_2)^+$ ion is envisaged as arising from the benzoxazine,^{50, 143} which would be formed from the oxirane, pathway *a*. This rearrangement has been achieved photochemically.⁸⁵ Alternatively the oxirane may rearrange to a 1-arylisatin, which can then lose two molecules of carbon monoxide, pathway *b*. An alternative decomposition of the benzoxazine gives the RCO^+ ion, pathway *c* (Scheme 15).

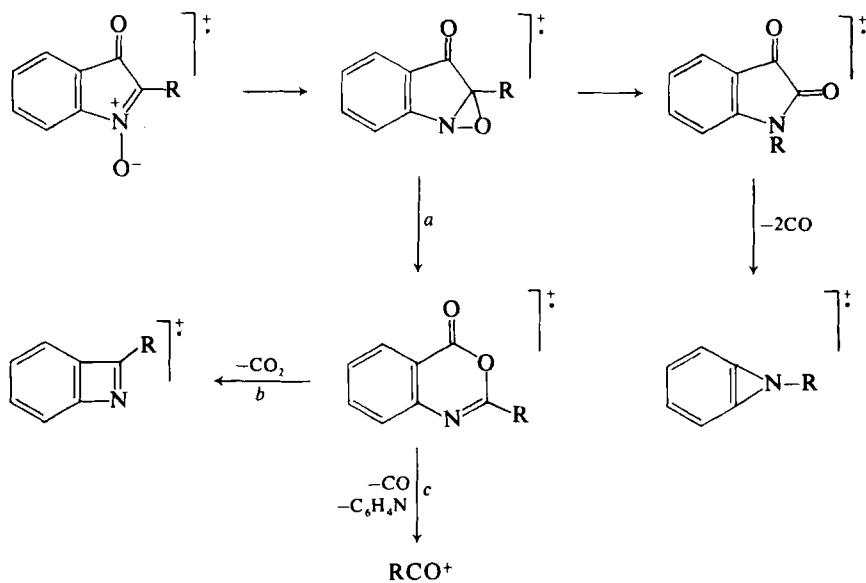
TABLE IV
FRAGMENTATION OF ISATOGENS ON ELECTRON IMPACT^{18, 19}

R=	% Ion abundance							
	M ⁺	(M-O) ⁺	(M-OH) ⁺	(M-CO) ⁺	(M-CHO) ⁺	(M-CO ₂) ⁺	(M-2CO) ⁺	RCO ⁺
Phenyl	100	12	51	5	3	11	17.7	12 ¹⁸
	100	14	59	10	—	9	17.5	14 ¹⁴³
2-Methylphenyl	33	22	100	4	9	16	14 ^a	10
4-Nitrophenyl	100	15	48	—	—	14	—	4
4-Methoxyphenyl	100	33	30	—	—	39	—	52
2-Pyridyl	100	29	26	2	6	17	9	—
CO ₂ Me	100	6	—	—	3	4	—	—

^a Actually (M-2CO-H)⁺ present due to ready loss of H from CH₃ group.



SCHEME 14



SCHEME 15

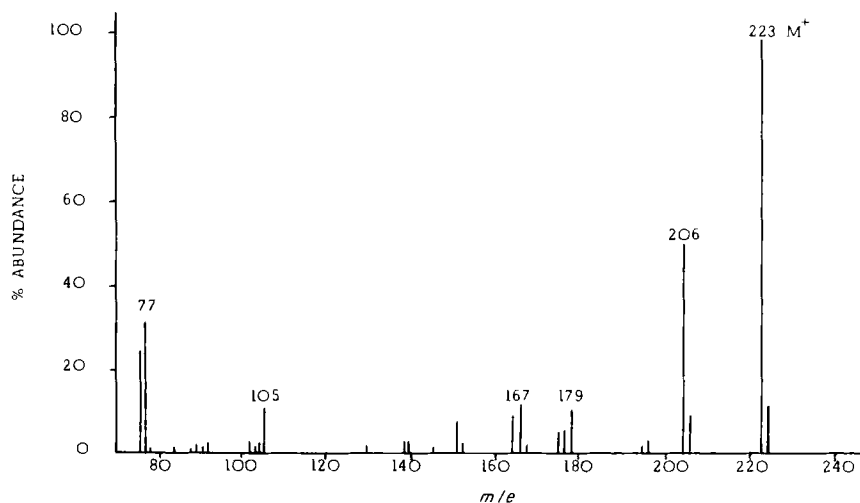


FIG. 4. Mass spectrum of 2-phenylisatogen.

VII. The Biological Properties of Isatogens and Indolones

2-Arylisatogens show significant antimicrobial activity against bacteria,³¹ mycoplasma organisms, and the mold *Candida albicans*.¹⁸ No useful biological activity has been observed with indolones.⁴⁹

A detailed study of the biochemical effects of 2-phenylisatogen (**209**: R = Ph) and 2-phenylindolone (**158**: R = Ph) shows that they both possess a range of action on mitochondrial respiration. Both compounds inhibit uptake of phosphate, glutamate, and calcium ions into mitochondria. 2-Phenylindolone is the more active. The effect on phosphate transport closely resembles that of organic mercury compounds, which are known to interact with thiol groups. It is suggested that the effect on phosphate transport of both 2-phenylindolone and 2-phenylisatogen arises from their ability to react with thiol compounds^{144,145} (Sections III,A,1 and V,A,1). The inhibition of oxidative phosphorylation by both these compounds, originally thought to be analogous to the action of aurovertin and oligomycin, is now recognized to arise from the blockade of phosphate transport.¹⁴⁴⁻¹⁴⁶ In contrast, 2-phenylcarbamoylisatogen (**209**: R = CONHPh) acts as a classical uncoupling agent and releases the inhibition of ATP synthesis caused by 2-phenylisatogen and oligomycin.¹⁴⁷ The change in activity following such a simple structural

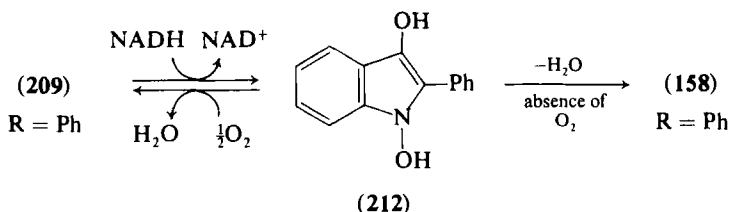
¹⁴⁴ A. P. Green, Ph.D. Thesis C.N.A.A. Sunderland Polytechnic, 1973.

¹⁴⁵ A. P. Green, M. Hooper, and A. J. Sweetman, *FEBS. Lett.* **33**, 297 (1973).

¹⁴⁶ A. P. Green, M. Hooper, and A. J. Sweetman, *FEBS. Lett.* **14**, 306 (1971).

¹⁴⁷ A. P. Green, M. T. Khatib, and A. J. Sweetman, *Biochem. Soc. Trans.* **2**, 953 (1974).

change is worth further investigation. 2-Phenylindolone inhibits the transhydrogenase system of submitochondrial particles which oxidize NADH, and succinate in the presence of ATP. This effect resembles that of *N*-ethylmaleimide and organic mercury compounds which are known to act by blocking active thiol groups.¹⁴⁸ 2-Phenylisatogen, which oxidizes thiol compounds, has a similar effect on this transhydrogenase system only when the mitochondrial particles are prepared in the presence of the isatogen. This observation has been used in locating the site of this enzyme system on the outside of the inner mitochondrial membrane.¹⁴⁹



In this latter case, however, the picture is complicated by the ability of 2-phenylisatogen to function as a hydrogen acceptor in the mitochondrial oxidation of NADH. This effect is not due to the direct oxidation of NADH by the isatogen and in the presence of oxygen 2-phenylindolone is not formed (cf. Section III,B). It is proposed that under these conditions 2-phenylisatogen acts as a reversible hydrogen carrier by formation of the unstable dihydroxyindole (212). In the absence of oxygen 2-phenylindolone is formed by an irreversible step. 2-Methyl-1,4-naphthoquinone, which has a similar redox potential to 2-phenylisatogen (Fig. 2, Section III,B), also has the same biochemical action.¹⁵⁰

Recently, a pharmacological study of the *p*-toluenesulfonic acid salt of 2-(2-pyridyl)isatogen has been reported. This compound is the first specific antagonist of ATP-induced relaxations of the guinea pig taenia caeci.¹⁵¹

¹⁴⁸ R. B. Beechey, K. J. Cattell, A. P. Green, M. Hooper, C. R. Lindop, and A. J. Sweetman, *Biochem. Soc. Trans.* **1**, 410 (1973).

¹⁴⁹ A. P. Green, M. Hooper, and A. J. Sweetman, *Biochem. Biophys. Res. Commun.* **58**, 337 (1974).

¹⁵⁰ A. P. Green, M. Hooper, and A. J. Sweetman, *Biochem. Pharmacol.* **23**, 1569 (1974).

¹⁵¹ M. Hooper, M. Spedding, A. J. Sweetman, and D. F. Weetman, *Proc. Brit. Pharmacol. Soc.*, 458 P (1974).

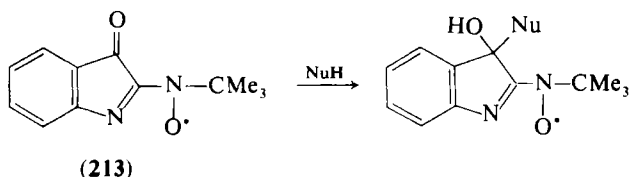
ACKNOWLEDGMENTS

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NOTE ADDED IN PROOF

A detailed study of the polarographic reduction of isatogens and indolones has been published.¹⁵² The results further substantiate Scheme 10 and Section III,B.

New indolones have been reported from the disproportionation of 1-chloromethylization.¹⁵³ A new class of indolones is represented by the free radical **213** which preferentially undergoes nucleophilic addition at the carbonyl group (cf. Sections V,A and E).¹⁵⁴



Diindolone (174) forms thiol adducts which are photochemically degraded to indigo.¹⁵⁵

Pyridyl isatogen tosylate (PIT) does not inhibit the excitatory action of exogenous ATP on the guinea pig ileum.¹⁵⁶ A further study of the uncoupler action of 2-phenyl-carbamoylisatogen has been published.¹⁵⁷

¹⁵² R. Andruzzi, A. Trazza, P. Bruni, and L. Greci, *Tetrahedron* **33**, 665 (1977).

¹⁵³ G. I. Zhungietu, L. P. Sinyavskaya, and T. Y. Filipenko, *Khim. Geterotsikl. Soedin.* No. 2, 217 (1977).

¹⁵⁴ H. G. Aurich and W. Weiss, *Justus Liebigs Ann. Chem.* **1976** (3), 432.

¹⁵⁵ C. Christopherson, F. Watjen, O. Buckhardt, and U. Anthoni, *Tetrahedron Lett.* 1747 (1977).

¹⁵⁶ T. Kazic and D. Milosavljevic, *J. Pharm. Pharmacol.* **29**, 542 (1977).

¹⁵⁷ A. P. Green, M. Hooper, and A. J. Sweetman, *Biochem. Biophys. Res. Commun.* **76**, 1166 (1977).

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The Chemistry of Aromatic Azapentalenes

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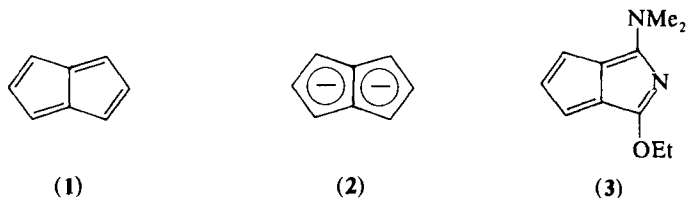
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I. Introduction

For the purposes of this review, aromatic azapentalenes may be broadly defined as heterocyclic analogs of pentalene (**1**)¹ which are aromatic by virtue of a 10- π -electron system; compounds of this type will thus be iso- π -electronic with the pentalene dianion (**2**).²

¹ For synthesis and properties of pentalenes, see: C. T. Blood and R. P. Linstead, *J. Chem. Soc.* 2255, 2263 (1952); C. C. Chuen and S. W. Fenton, *J. Org. Chem.* **23**, 1538 (1958); K. Hafner and J. Schneider, *Liebigs Ann. Chem.* **624**, 37 (1959); E. Le Goff, *J. Am. Chem. Soc.* **84**, 1505, 3975 (1962); K. Hafner, R. Fleischer, and K. Fritz, *Angew. Chem., Int. Ed. Engl.* **4**, 69 (1965); E. Müller, K. Munk, P. Ziemek, and M. Sauerbier, *Justus Liebigs Ann. Chem.* **713**, 40 (1968); K. Hartke and R. Matusch, *Chem. Ber.* **105**, 2584 (1972); S. A. R. Knox and F. G. A. Stone, *Acc. Chem. Res.* **7**, 321 (1974), and references therein.

² T. J. Katz and M. Rosenberger, *J. Am. Chem. Soc.* **84**, 865 (1962); T. J. Katz, M. Rosenberger, and R. K. O'Hara, *ibid.* **86**, 249 (1964).



The exact scope of systems covered is dealt with in Section II,C,1, but it is appropriate to mention here that 8- π -azapentalenes³⁻⁵ isoelectronic with pentalene (e.g., 3, the first stable 2-azapentalene⁴) will not be considered.

No specific review of aromatic azapentalenes exists, though much of the work before 1960 is covered in a more general article on bicyclic heterocycles with bridgehead nitrogen atoms by Mosby⁶ in the Weissberger series on heterocyclic chemistry. That article makes no distinction between "aromatic" and saturated systems, and the present review, though not exhaustive, deals mainly with aromatic systems and covers most of the literature to the end of 1975. Nonaromatic compounds will not be treated except where they are sufficiently important.

In the first part of this review we deal with the concept of heteroaromaticity and consider the aromaticity of heteropentalenes, particularly azapentalenes. Methods of synthesis, chemical reactivity, and spectroscopic properties are dealt with, and the review ends with a brief survey of their industrial uses and biological activity.

II. Heteroaromaticity

A. DEFINITION

Through its simplicity and ease of application, Hückel's rule,⁷ extended by Robinson⁸ to include p -doublets (electron pairs) of heteroatoms, has been an essential tool for the classification of aromatic

³ For syntheses and attempted syntheses of 8 π -azapentalene systems, see: (a) W. Treibs *Naturwissenschaften* **46**, 170 (1959) and (b) **48**, 130 (1961); (c) H. Paul and A. Weise, *Tetrahedron Lett.*, 163 (1963); (d) W. Treibs, *Chimia* **26**, 629 (1972); (e) H. R. Kwasnik, J. E. Oliver, and R. T. Brown, *J. Heterocycl. Chem.* **9**, 1429 (1972); (f) K. Hartke and S. Radau, *Annalen*, 2110 (1974); (g) D. G. Farnum, G. Mehta, G. G. I. Moore, and F. P. Segal, *Tetrahedron Lett.*, 2549 (1974).

⁴ K. Hafner and F. Schmidt, *Angew. Chem., Int. Ed. Engl.* **12**, 418 (1973).

⁵ H. Paul and A. Weise, *Z. Chem.* **4**, 147 (1964).

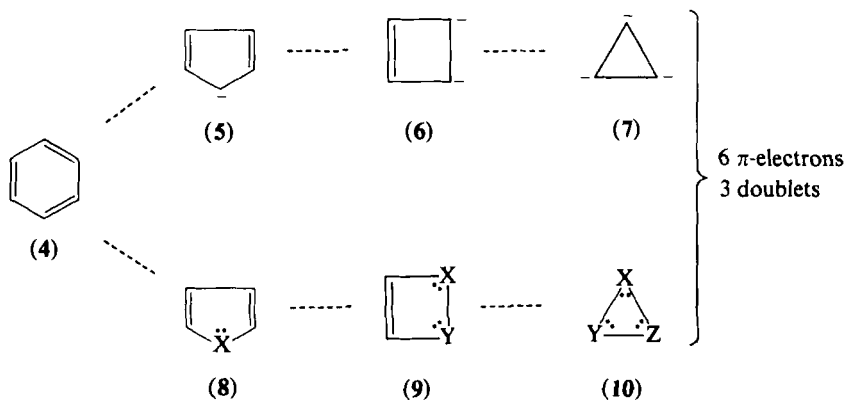
⁶ W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms" (A. Weissberger, ed.), Part I, p. 63. Wiley (Interscience), New York, 1961.

⁷ E. Hückel, *Z. Phys.* **70**, 204 (1931); **72**, 310 (1931).

⁸ R. Robinson, *Tetrahedron* **3**, 323 (1958).

heterocycles (e.g., into π -excessive and π -deficient species by Albert⁹), and for the prediction of new systems. The fact that Hückel's rule fits neatly into the concept of pericyclic reactions^{10, 11} allows us to propose the following definition of heteroaromaticity: A monocyclic or *o*-condensed polycyclic conjugated heterocycle will be aromatic if it possesses an odd number of *p*- or π -electron doublets. Using Kaneko's system of arrows,¹² an alternative form of this definition states: For a system to be aromatic, an odd number of arrows is needed to pass from one Kekulé structure to another.

The above definition is common usage, but most chemists who apply it have restricted themselves to cases where only one *p*-doublet derived from a heteroatom contributes to the π -system. The problem of aromaticity in heterocycles possessing more than one *p*-doublet has received comparatively little attention.^{13, 14} Scheme 1 shows two sequences, one homocyclic and the other heterocyclic, in which systems with three doublets are related to benzene.



SCHEME 1. X, Y, Z are O, N, or S.

All these systems are aromatic according to our proposed definition. To apply Kaneko's graphic method,^{12, 15} all the pairs of electrons must be used in a circular way (e.g., $6 \leftrightarrow 6' \leftrightarrow 6''$).

⁹ A. Albert, "Heterocyclic Chemistry." Athlone Press, London, 1959.

¹⁰ R. B. Woodward, Symposium on Orbital Symmetry Correlation in Organic Chemistry, Cambridge, (1969).

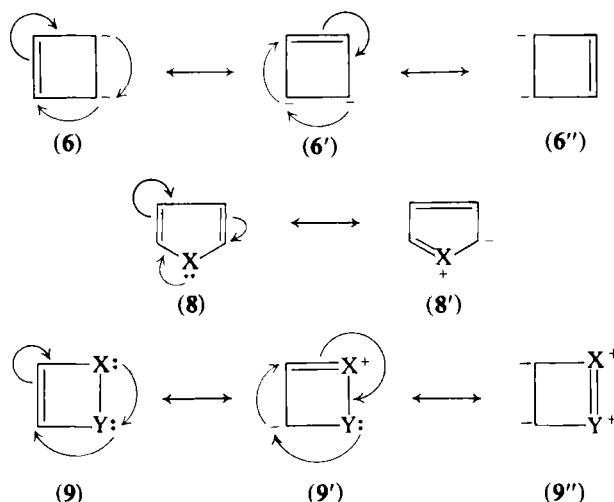
¹¹ J. Mathieu and A. Rassat, *Tetrahedron* **30**, 1753 (1974).

¹² C. Kaneko, *Tetrahedron* **28**, 4915 (1972).

¹³ M. E. Vol'pin, *Russ. Chem. Rev.* **29**, 129 (1960).

¹⁴ A. T. Balaban and Z. Simon, *Rev. Roum. Chim.* **10**, 1059 (1965).

¹⁵ C. Kaneko, S. Tanaka, and J. Elguero, unpublished work.



For systems **8**, dipolar canonical forms can be written (**8'**); and for **9**, the same process gives quadripolar structures (**9''**).

Our definition does not take account of lone pairs on heteroatoms in the ring which do not contribute to the π -system; we are normally concerned here with pyridinoid nitrogen atoms, and their influence on aromaticity is discussed in Section V,B. It is also noteworthy that for molecules possessing an unsubstituted pyrrole-type nitrogen atom, the aromaticity of the anion produced on deprotonation can be significantly greater than that of the protonated form. This has been found in a number of cases with aromatic annulenes,¹⁶⁻¹⁸ and we will meet similar results with certain mesoionic azapentalenes (Section IV,C,1,a).

Finally, if we abandon Hückel's topological approach altogether and consider more elaborate quantum-mechanical approaches, the concept of aromaticity derived purely from a consideration of π -electrons becomes blurred and tends to disappear completely. In fact, "all-electron" methods allow the calculation of "aromatic" properties (Section V,B) of a given substance without introducing explicitly the concept of aromaticity. Certain authors, notably Dewar,¹⁹ have published resonance energies derived from self-consistent field molecular-orbital (SCF-MO) calculations, and these could be used as a measure of aromaticity.

¹⁶ A. G. Anastassiou, *Acc. Chem. Res.* **5**, 281 (1972).

¹⁷ R. T. Seidner and S. Masamune, *Chem. Commun.*, 149 (1972); A. G. Anastassiou, R. L. Elliott, and E. Reichmanis, *J. Am. Chem. Soc.* **96**, 7823 (1974).

¹⁸ G. Schröder, G. Frank, H. Röttele, and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.* **13**, 205 (1974).

¹⁹ M. J. S. Dewar, A. J. Harget, and N. Trinajstić, *J. Am. Chem. Soc.* **91**, 6321 (1969).

B. AROMATICITY CRITERIA

This controversial topic has been the subject of an excellent review²⁰ by Cook, Katritzky, and Linda (hereafter abbreviated to CKL) in an earlier volume of this series. These authors tended to choose ground-state stability as a criterion for aromaticity, and this thermodynamic viewpoint is one used in the present article as well. Specific criteria used include tautomerism (CKL Section II,A,4), basicity (CKL Section II,A,5), and ring planarity (CKL Section II,B). The use of nuclear magnetic resonance (NMR) (CKL Section II,D) is more difficult, especially when systems with the same electronic structure but different numbers of pyridinoid nitrogen atoms are compared. In any case, semi-empirical CNDO (complete neglect of differential overlap) or INDO (intermediate neglect of differential overlap) calculations can provide chemical shifts and coupling constants for a given molecule without making any assumptions about its aromaticity.

The use of ground-state stability as a criterion poses problems when applied to charged species, but this does not normally prevent the cyclopentadienyl anion (**5**)²¹ or the cyclobutene dianion (**6**)²² from being classed as aromatic. The cyclopropane trianion **7** is unknown, and there are not even any calculations to indicate whether it would be reasonably stable. Among heterocycles, the experimental aromaticity of pyrrole (**8**: X = NH), the pyrrole anion (**8**: X = N⁻), furan (**8**: X = O), and thiophene (**8**: X = S) is still a controversial subject (CKL Section III,C,1 and ref. 23). As for four-membered systems isoelectronic with the cyclobutene dianion (**6**) (CKL Section III,B), their stability seems to depend on the nature of the heteroatoms X and Y: they are extremely unstable when X = Y = O, fairly unstable when X = Y = NR (a rigorous theoretical treatment is in progress^{24a}), and fairly stable when X = Y = S. Last, three-membered ring systems (**10**) are generally less stable than their open-chain dipolar isomers; in the case of di-*t*-butyloxadiaziridine (X = O, Y = Z = N-Bu-*t*) both isomers are known,^{24b} but in the case of trioxirane (X = Y = Z = O) the open-chain isomer, ozone, has been calculated (*ab initio* optimized geometries)^{24c} to be 18 kcal/mole more stable than the trioxirane.

²⁰ M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.* **17**, 255 (1974).

²¹ G. M. Badger, "Aromatic Character and Aromaticity," p. 82. Cambridge Univ. Press, London and New York, 1969.

²² J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *Chem. Commun.*, 365 (1972).

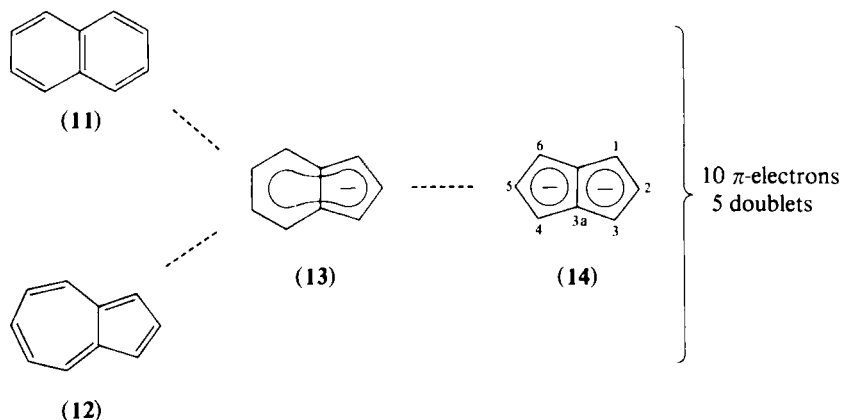
²³ P. Lazzeretti and F. Taddei, *Mol. Phys.* **27**, 1439 (1974); F. Fringuelli, G. Marino, A. Taticchi, and G. Grandolini, *J. Chem. Soc., Perkin Trans. 2*, 332 (1974); M. H. Palmer and R. H. Findlay, *Tetrahedron Lett.*, 253 (1974).

²⁴ (a) G. Leroy and J. M. Mangen, unpublished results; (b) S. S. Hecht and F. D. Greene, *J. Am. Chem. Soc.* **89**, 6761 (1967); (c) W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, and J. A. Pople, *Top. Current Chem.* **40**, 1 (1973).

C. AROMATIC AZAPENTALENES

1. Scope

We will now consider heterocycles with 5 doublets (10 π -electrons) of which at least two are *p*-doublets. Among monocyclic systems (i.e., analogs of the cyclooctatriene dianion²⁵ and the cycloheptadiene trianion²⁶) the compounds known are few and unstable (CKL Sections III,F and III,E,2). The present review is devoted to a study of a group of 10- π -electron bicyclic systems possessing two *p*-doublets: the aromatic azapentalenes. These compounds are isoelectronic with the pentalene dianion (**14**) (Scheme 2).



SCHEME 2

Just as there is a family of heterocycles isoelectronic with the indene monoanion (**13**)²⁷ (indole, isoindole, indolizine, pseudoazulenes, etc.), there are several hundred possible systems derived from the pentalene dianion (**14**).² Scheme 3 shows some examples (**15**–**20**) derived (formally) from each canonical form of **14**.

The fundamental interest in these structures has been remarked on by a number of workers, notably Babichev^{28, 29} (1963), who classed compound **19** as a heteroanalog of azulene (**12**), and Reid³⁰ (1965), who considered the same compound among "heterocycles isoelectronic with

²⁵ T. J. Katz, *J. Am. Chem. Soc.* **82**, 3784 (1960); H. P. Fritz and H. Keller, *Chem. Ber.* **95**, 158 (1962).

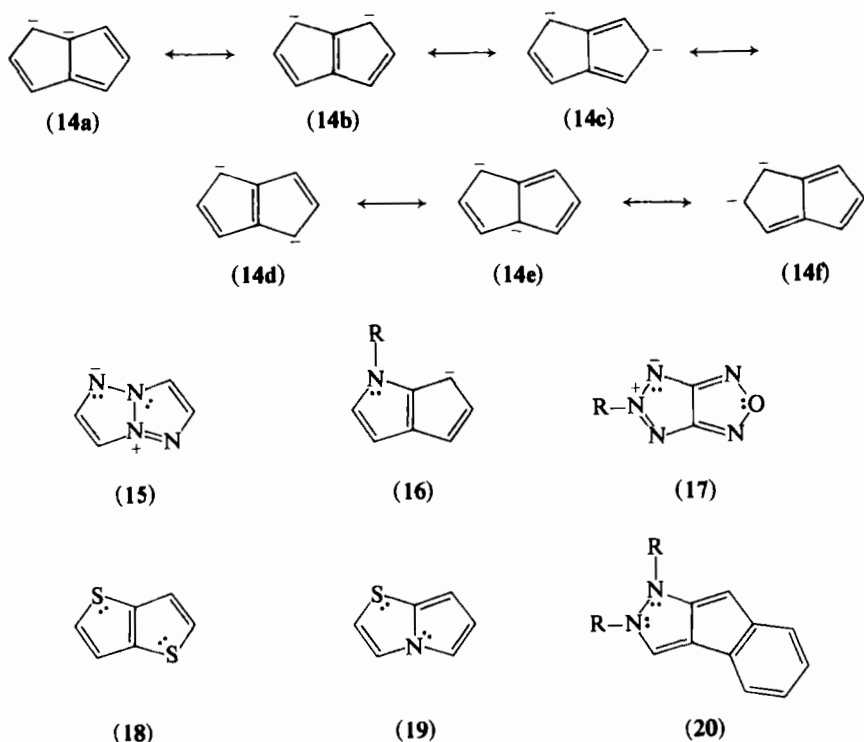
²⁶ This trianion has not yet been described.

²⁷ S. Wold and G. Bergson, *Ark. Kemi* **28**, 245 (1967).

²⁸ F. S. Babichev and V. K. Kibirev, *Zh. Obshch. Khim.* **33**, 2000 (1963).

²⁹ V. K. Kibirev and F. S. Babichev, *Ukr. Khim. Zh.* **30**, 488 (1964).

³⁰ B. B. Molloy, D. H. Reid, and F. S. Skelton, *J. Chem. Soc.*, 65 (1965).



SCHEME 3

indolizine and other bicyclic 10π -electron structures.” The work of Katz^{31a} (1967) on azapentalene anions **246** and of Boekelheide³² (1968) on the first theoretical treatment of diazapentalene **214** and the studies of the E.I. du Pont de Nemours team (CKL Section III,H,5) on tetrazapentalenes of type **15** are also worthy of mention. As Binsch³³ remarked: “Molecules having the topology of the pentalene system and containing nitrogen atoms in the bridgehead positions are also called azapentalenes in the literature, but they are really analogs of the pentalene dianion, an aromatic system.”

2. Limitations

Since the number of possible ring systems derived from **14** is very large, we have decided to limit this review to azapentalenes whose

³¹ (a) W. H. Okamura and T. J. Katz, *Tetrahedron* **23**, 2941 (1967); (b) E. E. Schweizer and K. K. Light, *J. Org. Chem.* **31**, 2912 (1966).

³² V. Boekelheide and N. A. Fedoruk, *J. Am. Chem. Soc.* **90**, 3830 (1968).

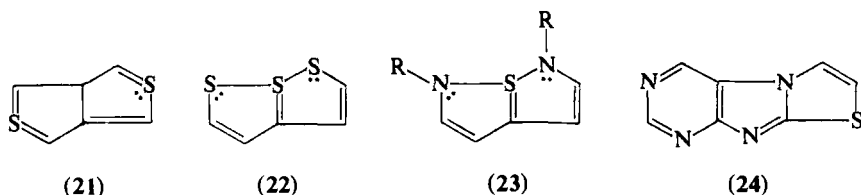
³³ G. Binsch and I. Tamir, *J. Am. Chem. Soc.* **91**, 2450 (1969).

structures are given by the selection rules in Scheme 4. Three parts of the ring are considered: the atoms providing the p -doublets, the atom at the ring junction, and the atoms on the periphery.

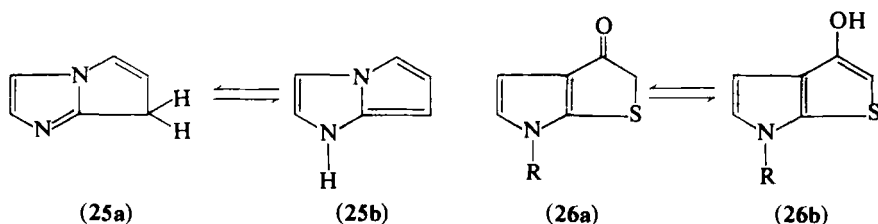
Two doublets	: one \tilde{N} , the other C^- , N^- , \tilde{N} , \tilde{O} , \tilde{S}
Atoms at ring junction	: C or N^+
Atoms on periphery	: C, N or N^+ (also 2 adjacent carbons as part of a benzene ring)

SCHEME 4

Systems outside the scope of this review are, for example: (a) those in which no N-doublets contribute to the π -system; these include thienothiophenes **18** and **21** (cf. CKL Section III,H,4 and ref. 34); (b) compounds with sulfur or oxygen at the ring junction, such as trithiapentalenes (**22**)³⁵ and 6a-thia-1,6-diazapentalenes (**23**),³⁶ and (c) systems with a third fused heterocyclic ring, e.g., thiazolo[3,2-c]purines (**24**).³⁷



However, certain nonaromatic compounds are included, e.g., **25a**³⁸ and **26a**³⁹ for which it is possible to write aromatic tautomers (**25b** and **26b**).



³⁴ M. P. Cava and M. V. Lakshmikantham, *Acc. Chem. Res.* **8**, 139 (1975); V. P. Litvinov and Ya. L. Gol'dfarb, *Adv. Heterocycl. Chem.* **19**, 123 (1976).

³⁵ N. Lozac'h, *Adv. Heterocycl. Chem.* **13**, 161 (1971).

³⁶ A. S. Ingram, D. H. Reid, and J. D. Symon, *J. Chem. Soc., Perkin Trans. 1*, 242 (1974).

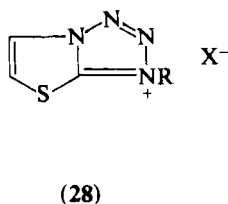
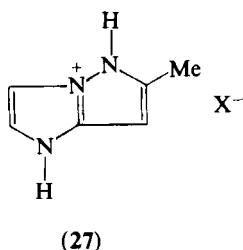
³⁷ H. Uno, A. Irie, and K. Hino, *Chem. Pharm. Bull.* **21**, 34 (1973).

³⁸ P. M. Kochergin, Y. N. Sheinker, A. A. Druzhinina, R. M. Palei, and L. M. Alekseeva, *Khim. Geterotsikl. Soedin.* **7**, 826 (1971).

³⁹ E. T. Holmes and H. R. Snyder, *J. Org. Chem.* **29**, 2725 (1964).

3. Classification

A classification according to the six structures in Scheme 3 is meaningless for compounds that are themselves anions (since the negative charges on the anions shown in Scheme 3 are arbitrarily located) and not very useful for neutral systems. A subdivision into anions (e.g., **16**), neutral molecules (e.g., **19** and **20**), mesoionic systems (e.g., **15** and **17**), and cations (e.g., **27**⁴⁰ and **28**⁴¹), though important when considering reactivity, is also inadequate.



We have therefore decided to ignore the total charge carried by the ring and classify compounds into the following three groups:

- A. Azapentalenes lacking a nitrogen atom at the ring junction (1-aza or 2-aza series), e.g., **16**, **17**, **20**.
- B. Azapentalenes with one nitrogen atom at the ring junction (3a-aza series), e.g., **19**, **25**, **27**, **28**.
- C. Azapentalenes with two nitrogen atoms at the ring junction (3a,6a-diaza series), e.g., **15**.

III. Synthesis

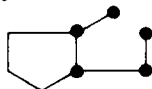
A wide variety of methods for the synthesis of aromatic azapentalenes have been reported, and, to rationalize these, we shall deal with compounds of types A, B, and C (Section II,C,3) separately and classify synthetic routes to each type according to the number of new bonds formed in the reaction (Scheme 5).

In some ways this classification is arbitrary since, for example, the formation of **30** could be catalogued as [3 + 2] according to the overall synthesis, or as [5 + 0] if cyclization of the intermediate **29** is considered. We have often tried to classify a synthesis according to the

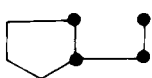
⁴⁰ L. Knutsson and J. Elguero, unpublished results.

⁴¹ H. Alper and R. W. Stout, *J. Heterocycl. Chem.* **10**, 5 (1973).

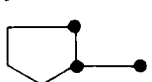
– [5 + 0] Syntheses:



– [4 + 1] Syntheses:



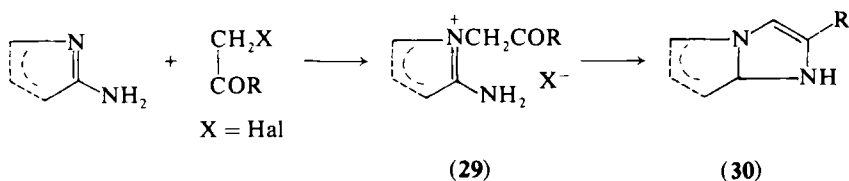
– [3 + 2] Syntheses:



– Formation of both rings simultaneously.

SCHEME 5. Classification system for syntheses.

last step, but it has sometimes been convenient to place a particular method in a different category to preserve continuity. Since much of this part of the review is little more than a catalog of reactions, a short section (D) devoted to general remarks is included at the end.



A. AZAPENTALENES LACKING A RING JUNCTION NITROGEN ATOM (TYPE A)

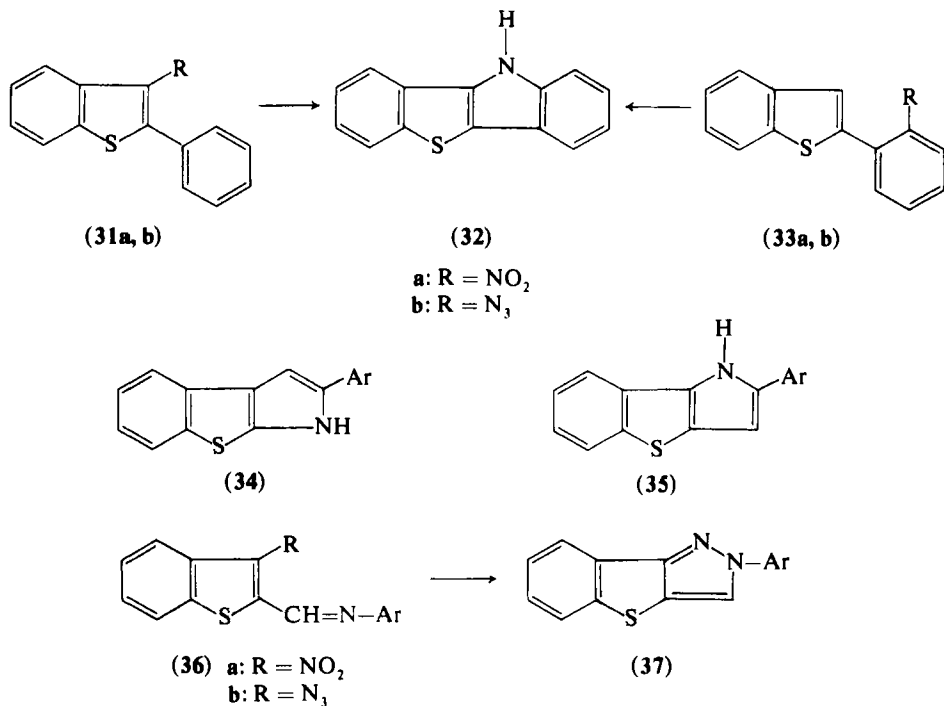
1. [5 + 0] Syntheses

a. *Intramolecular Cyclization of Nitrene Intermediates.* A number of systems have been prepared by cyclization of nitrenes generated by treatment of nitro compounds with triethyl phosphite (TEP). These include benzo[*b*]thieno[3,2-*b*]indoles (32) by reductive cyclization of the nitrothiophene (31a) or the nitrophenyl derivative (33a),^{42, 43} 2-aryl-1H-

⁴² K. E. Chippendale, B. Iddon, and H. Suschitzky, *Chem. Commun.*, 203 (1971).

⁴³ K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 2023 (1972).

[1]benzothieno[2,3-*b*]pyrroles (**34**) from *trans*-1-aryl-2-(2-nitro-3-benzo-*[b]*thienyl)ethene, and 2-aryl-1*H*-[1]benzothieno[3,2-*b*]pyrroles (**35**) from *trans*-1-aryl-2-(3-nitro-2-benzo-*[b]*thienyl)ethene.⁴⁴ Thieno[2,3-*b*]pyrroles and thieno[3,2-*b*]pyrroles, analogs of **34** and **35** lacking an annelated benzene ring, were prepared from similar starting materials.⁴⁵ The fused pyrazoles **37** were prepared by treating *N*-(3-nitrobenzo-*[b]*-thien-2-ylidene)anilines (**36**) with TEP.⁴⁶



The *N*-phenyl derivative (**37**: Ar = Ph) was obtained in higher yield (45%) when the corresponding anil (**36a**) was heated with triphenylphosphine in *p*-cymene.⁴⁶

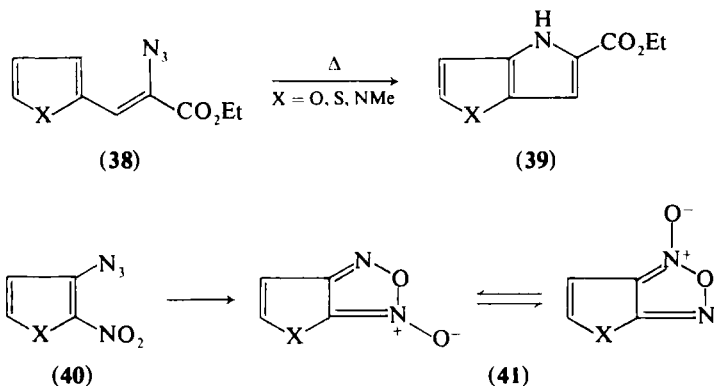
Thermally generated nitrene intermediates cyclize in the same way; thus **32** was prepared from the azides **31b** or **33b** in diglyme,^{42, 43} and thermal ring closure of azide derivatives **36b** in bis-(2-methoxyethyl) ether afforded **37** in 70–75% yield.⁴⁶ Other examples include the

⁴⁴ K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans 1*, 125 (1973).

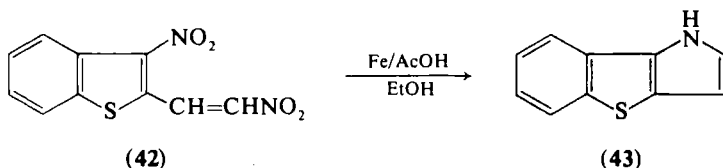
⁴⁵ K. Srinivasan, K. G. Srinivasan, K. K. Balasubramanian, and S. Swaminathan, *Synthesis*, 313 (1973).

⁴⁶ K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 129 (1973).

preparation of the fused pyrroles **39** ($X = \text{NMe}$) from the corresponding azidoacrylates **38**⁴⁷ and the low-yield synthesis of thieno[2,3-*c*]furan oxide⁴⁸ (**41**, $X = \text{S}$) from the thiophene (**40**; $X = \text{S}$). Even though compound **41** ($X = \text{S}$) is not an azapentalene included in this review (Section II,C,2) the synthesis could be extended to azidoazoles **40** ($X = \text{NR}$).



Reduction of 3-nitro-2-(ω -nitrovinyl)benzo[*b*]thiophene (**42**) with iron and acetic acid in ethanol gave **43**.^{49, 50}



b. Intramolecular Cyclization of an Amino Group. Various acidic reagents have been used to effect ring closure by condensation of an amino substituent with a suitably placed carbonyl group. Indolo[3,2-*b*]indole (**45**) was obtained by reductive dehydration of **44** with stannous chloride,⁵ and the same reagent caused cyclization of ethyl-3-nitro-2-thienyl pyruvate (**46**) to the thieno[3,2-*b*]pyrrole (**47**) via the intermediate aminothiophene.^{51a}

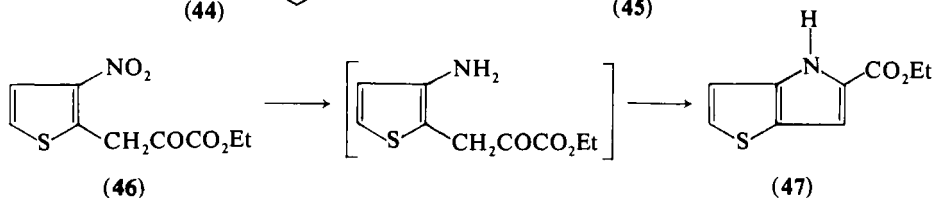
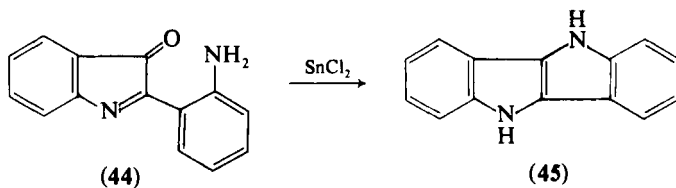
⁴⁷ H. Hemetsberger and D. Knittel, *Monatsh. Chem.* **103**, 194 (1972); K. N. Java, S. Soth, M. Farnier, and C. Paulmier, *C.R. Hebd. Seances Acad. Sci., Ser. C.* **281**, 793 (1975).

⁴⁸ A. J. Boulton and D. Middleton, *J. Org. Chem.* **39**, 2956 (1974).

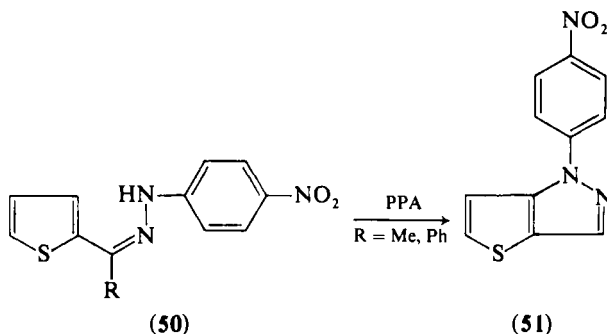
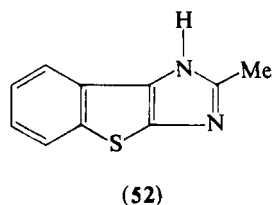
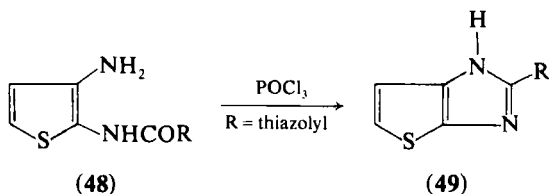
⁴⁹ O. P. Shkurko and V. P. Mamaev, *Khim. Geterotsikl. Soedin.* **2**, 634 (1966).

⁵⁰ O. P. Shkurko and V. P. Mamaev, *Izv. Sib. Akad. Nauk. SSSR, Ser. Khim. Nauk.* **2**, 112 (1967) [*CA* **69**, 27290 (1968)].

⁵¹ (a) W. W. Gale, A. N. Scott, and H. R. Snyder, *J. Org. Chem.* **29**, 2160 (1964); (b) E. T. Holmes and H. R. Snyder, *ibid.* **29**, 2155 (1964).



Direct cyclization of a related aminothiophene (48) occurred on treatment with phosphorus oxychloride to give 49,⁵² and ring closure between the thiophene ring and the side chain in the *p*-nitrophenylhydrazones (50) with polyphosphoric acid yielded 51.⁵³ On heating, 2,3-diacetamidobenzo[*b*]thiophene eliminated acetic acid and water to give 2-methylbenzothieno[2,3-*d*]imidazole (52),^{54,55} but successful conditions could not be found for cyclization of 2-acetamido-3-phenylaminobenzo[*b*]thiophene.⁵⁵



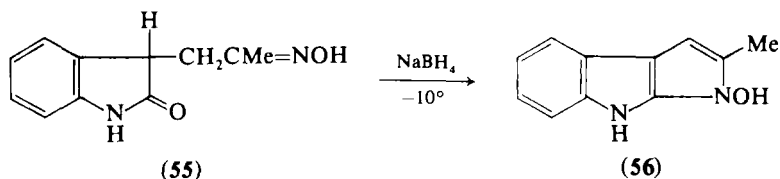
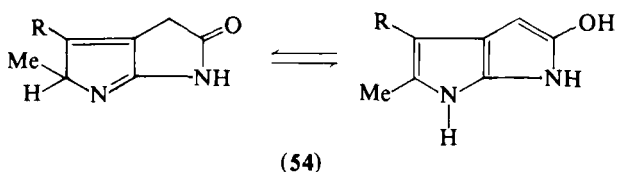
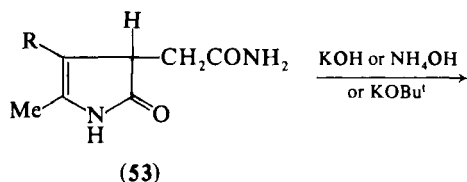
⁵² D. R. Hoff and L. H. Peterson, S. African Patent 6,800,904 (1969) [CA 72, 100702 (1970)].

⁵³ E. B. Dennler and A. R. Frasca, *Can. J. Chem.* **45**, 697 (1967).

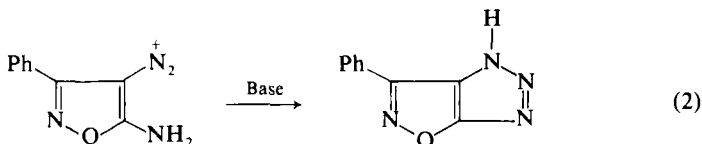
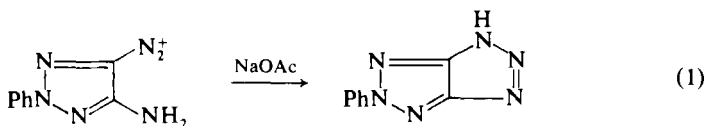
⁵⁴ V. G. Zhiryakov and P. I. Abramenko, USSR Patent 224,524 (1968) [CA 70, 20060 (1969)].

⁵⁵ P. I. Abramenko, *Khim. Geterotsikl. Soedin.* **6**, 1473 (1970).

A series of pyrrolopyrroles **54** were prepared by cyclization of the amide **53** under basic conditions,⁵⁶ and recently, cyclization of the related oxindole **55** was reported⁵⁷ to give an analogous system **56**.



c. *Cyclization of an Azo or Diazonium Group.* Typical examples of this method involve formation of the *v*-triazole ring by cyclization of a diazonium group to an adjacent amino group under mildly basic conditions [Eqs. (1) and (2)].⁵⁸⁻⁶⁰



⁵⁶ C. de Witt Blanton, J. F. Whidby, and F. H. Briggs, *J. Org. Chem.* **36**, 3929 (1971).

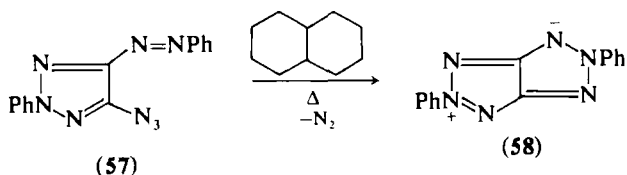
⁵⁷ N. Shoji, Y. Kondo, and T. Takemoto, *Heterocycles* **1**, 251 (1973).

⁵⁸ J. Thiele and K. Schleussner, *Justus Liebigs Ann. Chem.* **295**, 129 (1897).

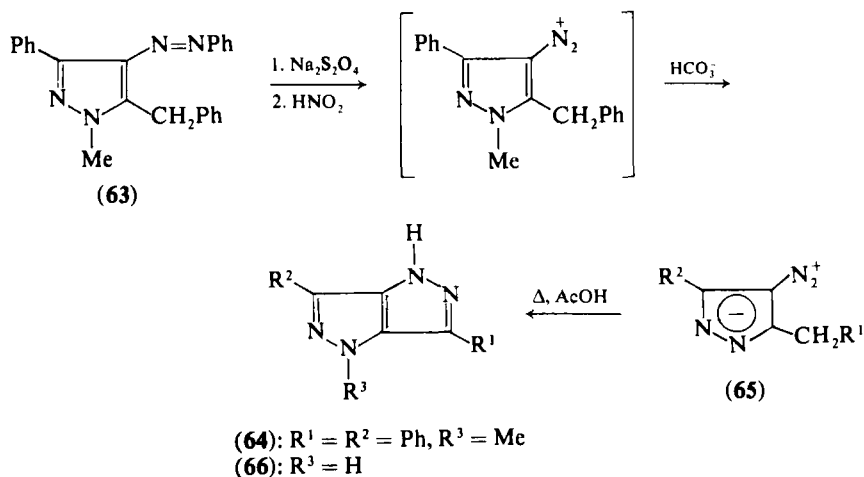
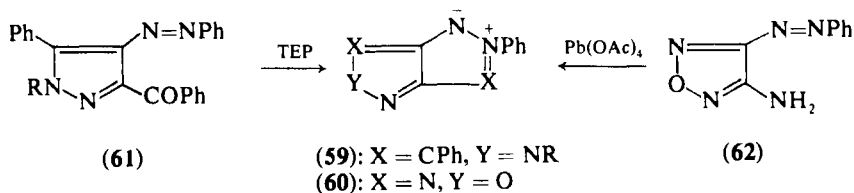
⁵⁹ H. Wieland and F. Gmelin, *Justus Liebigs Ann. Chem.* **375**, 297 (1910).

⁶⁰ G. Desimoni and G. Minoli, *Tetrahedron* **26**, 1393 (1970).

The *v*-triazole ring is also produced by intramolecular cyclization of an azide substituent to an azo group; in this way the mesoionic *v*-triazolo[4,5-*d*]-*v*-triazole (**58**) was obtained by heating 4-azido-2-phenyl-5-phenylazo-*v*-triazole (**57**) in decalin.⁶¹



Two closely related mesoionic systems, **59** and **60**, were obtained by reductive cyclization of **61** with TEP,⁶² and by oxidation of **62** with lead tetraacetate,⁶³ respectively. The pyrazolo[4,3-*c*]pyrazole **64** was obtained from the azo compound **63** by reduction with dithionite, followed by diazotization of the resultant amine and cyclization with



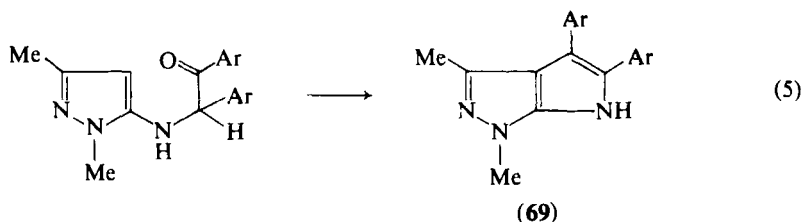
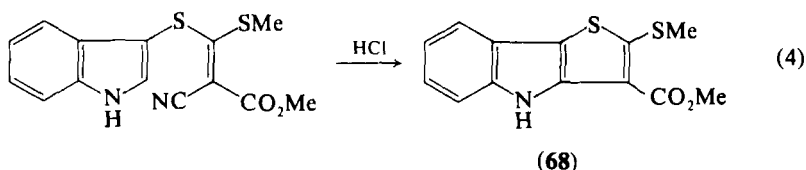
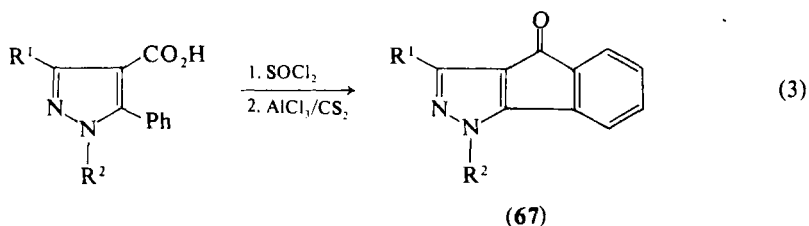
⁶¹ M. Yoshida, A. Matsumoto, and O. Simamura, *Bull. Chem. Soc. Jpn.* **43**, 3587 (1970).

⁶² J. H. Lee, A. Matsumoto, M. Yoshida, and O. Simamura, *Chem. Lett.*, 951 (1974).

⁶³ A. Matsumoto, M. Yoshida, and O. Simamura, *Bull. Chem. Soc. Jpn.* **47**, 1493 (1974).

bicarbonate,⁶⁴ and derivatives of the same ring system **66** resulted from thermal ring closure of the pyrazole **65**.^{65, 66} For this latter reaction, Farnum and Yates⁶⁵ suggest a radical mechanism involving hydrogen abstraction from the methylene group as the first step.

d. *Miscellaneous Syntheses.* Cyclizations between an exocyclic carbonyl group or cyano group and a ring carbon atom have been used to produce indenopyrazoles (**67**),⁶⁷ thienoindoles (**68**),⁶⁸ and pyrrolopyrazoles (**69**)⁶⁹ as shown in Eqs. (3)–(5).



⁶⁴ J. H. Lee, A. Matsumoto, M. Yoshida, and O. Simamura, *Bull. Chem. Soc. Jpn.* **47**, 1039 (1974).

⁶⁵ D. G. Farnum and P. Yates, *J. Am. Chem. Soc.* **84**, 1399 (1962).

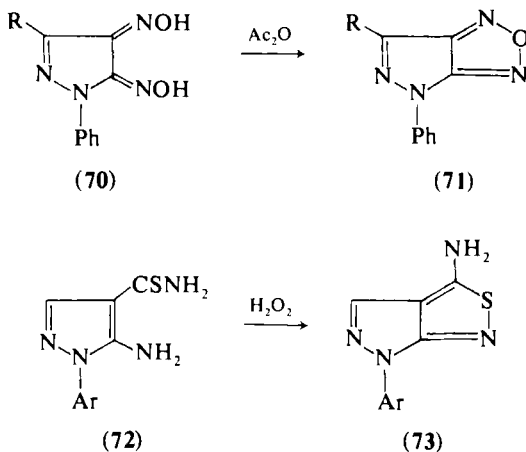
⁶⁶ (a) G. Fukata, Y. Kawazoe, and T. Taguchi, *Tetrahedron Lett.*, 1199 (1973); (b) *Yakugaku Zasshi* **94**, 17 (1974) [*CA* **81**, 63543 (1974)]; (c) **94**, 23 (1974) [*CA* **80**, 108437 (1974)]; (d) **94**, 36 (1974) [*CA* **80**, 108434 (1974)].

⁶⁷ K. Arakawa, Japanese Patent 7,432,533 (1974) [*CA* **82**, 140130 (1975)].

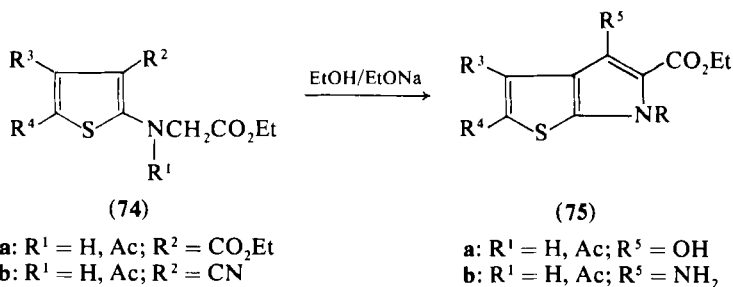
⁶⁸ (a) G. Kobayashi, Y. Tominaga, S. Kisaki, M. Sone, and S. Ueno, *Chem. Pharm. Bull.* **21**, 2344 (1973); (b) S. Kisaki, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *ibid.* **22**, 2246 (1974).

⁶⁹ L. R. Swett and G. Y. Paris, German Patent 2,205,136 (1972) [*CA* **77**, 140059 (1972)].

Pyrazolo[3,4-*c*]furazans (**71**) have been prepared by dehydration of dioximinopyrazolines **70**,⁷⁰ and fused isothiazoles **73** by oxidative cyclization of thioamides **72**⁷¹ following adaptations of standard syntheses of furazans and isothiazoles.



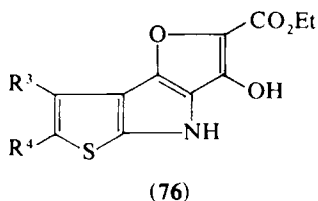
Ring closure of certain thiophene diesters **74a** or cyanoesters **74b** under Dieckmann conditions (EtOH/EtONa) has recently been shown to give thieno[2,3-*b*]pyrroles (**75a, b**) in high yield (65–90%).⁷² A thieno[2,3-*b*]pyrrole diester (**75**: $\text{R}^5 = \text{OCH}_2\text{CO}_2\text{Et}$) prepared in this way failed to undergo further cyclization to the tricyclic system **76** under the same conditions.^{72b}



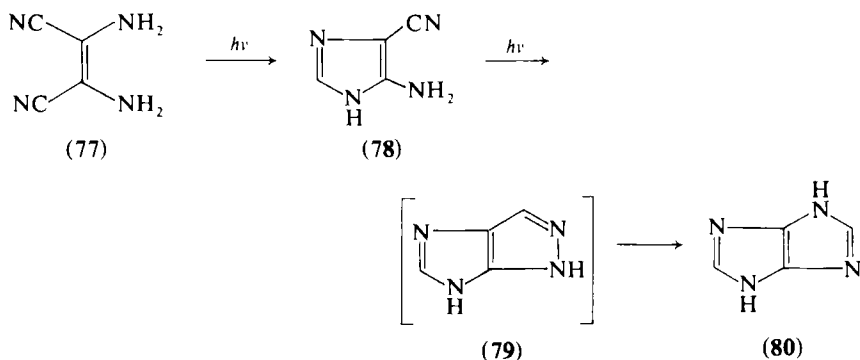
⁷⁰ R. C. Bertelson, K. D. Glanz, and D. B. McQuain, *J. Heterocycl. Chem.* **6**, 317 (1969).

⁷¹ T. Irikura, K. Kasuga, K. Ushiyama, and S. Sato, Japanese Patent 7,427,596 (1974) [CA **82**, 125401 (1975)].

⁷² (a) R. A. Crochet, J. T. Boatright, C. De Witt, Blanton, C. T. Wie, and W. E. Hochholzer, *J. Heterocycl. Chem.* **11**, 143 (1974); (b) M. Wierzbicki, D. Cagniant, and P. Cagniant, *Bull. Soc. Chim. Fr.*, 1786 (1975).



Ferris and Antonucci⁷³ have reported a photochemical synthesis of imidazo[4,5-*d*]imidazole (**80**) from 4-aminoimidazole-5-carbonitrile (**78**), which has attracted interest since **78**, and its photochemical precursor diaminomaleonitrile (**77**) have been proposed⁷⁴ as key intermediates in the prebiotic chemical evolution of purines. Mechanistic studies^{73b} suggest that the fused pyrazole **79** may be an intermediate.



2. [4 + 1] Syntheses

In this section, all the examples from the literature involve the introduction of one heteroatom to create the new five-membered ring.

Introduction of a sulfur atom has been effected in many cases with phosphorus pentasulfide; for example, ring closure of 1,4-dicarbonyl compounds **81** ($X = \text{CH}$) under typical Paal-Knorr conditions gives fused thiophenes **82** ($X = \text{CH}$).^{75, 76} Fused thiazoles [**82** ($X = \text{N}$) and Eqs. (6), (7)] have been prepared in the same way.⁷⁷⁻⁸⁰

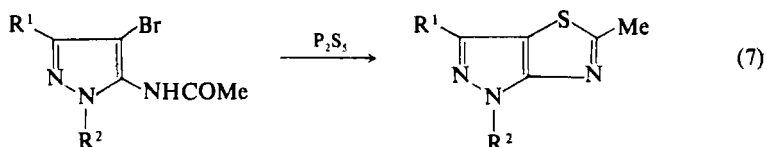
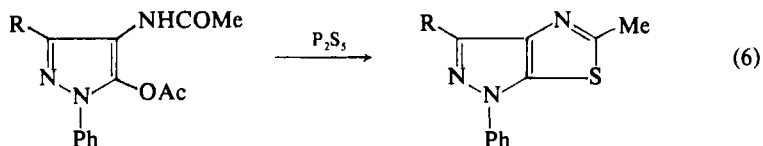
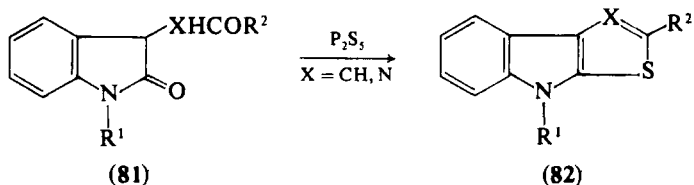
⁷³ (a) J. P. Ferris and F. R. Antonucci, *Chem. Commun.*, 126 (1972); (b) *J. Am. Chem. Soc.* **96**, 2010 (1974); (c) **96**, 2014 (1974).

⁷⁴ R. A. Sanchez, J. P. Ferris, and L. E. Orgel, *J. Mol. Biol.* **38**, 121 (1968).

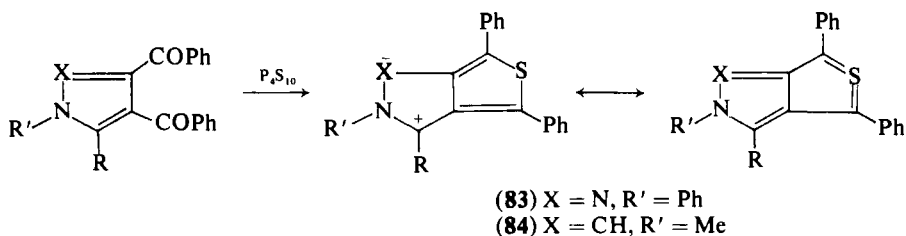
⁷⁵ G. Kobayashi, S. Furukawa, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi* **89**, 58 (1969) [*CA* **70**, 96665 (1969)].

⁷⁶ G. Kobayashi and Y. Matsuda, Japanese Patent 7,236,757 (1972) [*CA* **77**, 140005 (1972)].

⁷⁷ (a) P. I. Abramenko, *Zh. Vses. Khim. Obschest.*, **16**, 231 (1971) [*CA* **75**, 5778 (1971)]; (b) **18**, 714 (1973) [*CA* **80**, 95808 (1974)].



Potts and McKeough⁸¹ have recently obtained several interesting mesoionic azapentalenes **83**, **84** by reaction of the appropriate 1,4-dicarbonyl compound with phosphorus pentasulfide. Compounds **83** and **84** can be written as dipolar structures, but participation of sulfur *d*-orbitals allows nonpolar forms to be envisaged. MO calculations neglecting *d*-orbital participation predict the thieno[3,4-*c*]pyrrole system (**84**) to be very unstable.⁴³⁰ A related system **86** has been prepared by Japanese workers⁶³ from the diamino-*v*-triazole (**85**) and sulfur dichloride.

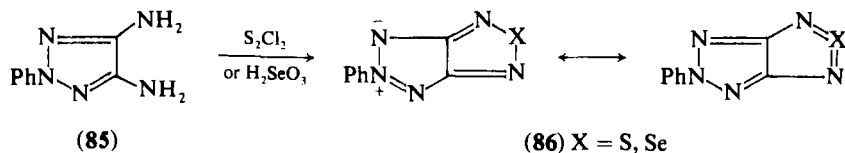


⁷⁸ Z. I. Miroshnichenko and M. A. Al'perovich, USSR Patent 161,765 (1964) [CA **61**, 3177 (1964)].

⁷⁹ Z. I. Miroshnichenko and M. A. Al'perovich, *Khim. Geterotsikl. Soedin.* **1**, 254 (1965).

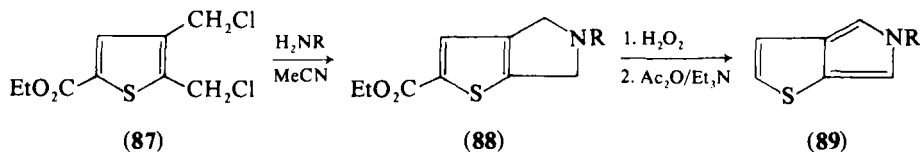
⁸⁰ (a) Z. I. Moskalenko and M. A. Al'perovich, USSR Patent 178,381 (1966) [CA **64**, 19628 (1966)]; (b) Z. I. Moskalenko and G. P. Shumelyak, *Khim. Geterotsikl. Soedin.* **10**, 932 (1974).

⁸¹ K. T. Potts and D. McKeough, *J. Am. Chem. Soc.* **96**, 4268, 4276 (1974).

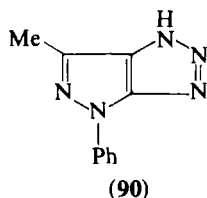


Thionyl chloride has been used to introduce a sulfur atom in the preparation of an isothiazolo[4,5-*b*]indole derivative from *N*-1-dimethyl indole-2-carboxamide.^{82,83}

Introduction of the nitrogen atom in **89** was achieved⁸⁴ by reaction of the 1,4-dichloro derivative **87** with a primary amine in acetonitrile to give initially the nonaromatic system **88**. Aromatization was effected through dehydration of the *N*-oxide by a method due to Kreher and Seubert,⁸⁵ used originally for the preparation of *N*-substituted isoindoles.



The *v*-triazole ring in the pyrazolo[3,4-*d*]-*v*-triazole (**90**) was generated by nitrosation of 4,5-diamino-3-methyl-1-phenylpyrazole.⁸⁶



3. [3 + 2] Syntheses

a. *Halogen Displacement by Nucleophiles.* Various fused pyrazoles have been obtained by modifications of standard methods as shown in Eqs. (8) and (9),⁸⁷⁻⁹⁰ and in a similar way carbanions generated from β -

⁸² I. I. Grandberg and G. V. Klyuchko, *Zh. Obshch. Khim.* **32**, 1898 (1962).

⁸³ (a) J. Szmuszkovicz, U.S. Patent 3,147,273 (1964) [*CA* **61**, 14676 (1964)]; (b) J. Szmuszkovicz, *J. Org. Chem.* **29**, 178 (1964).

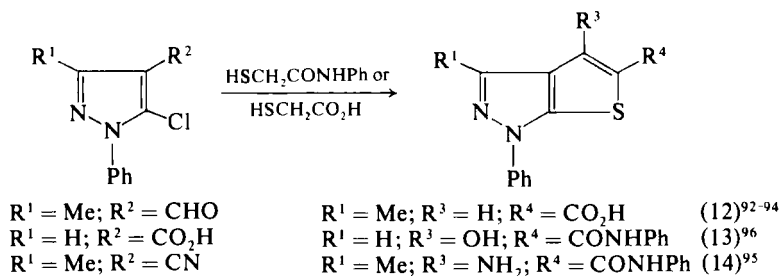
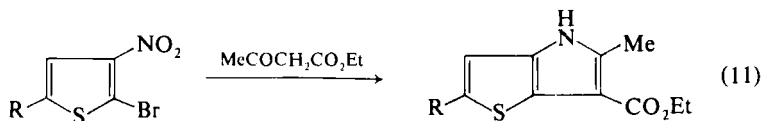
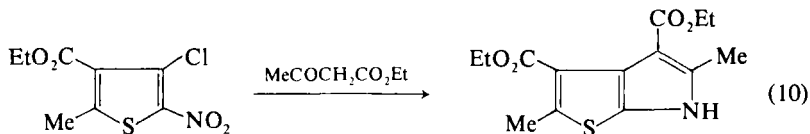
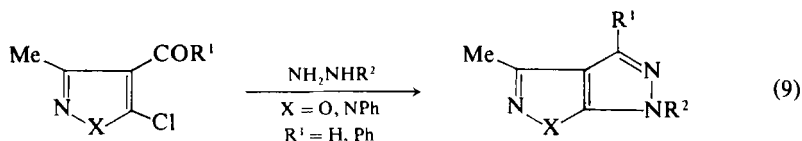
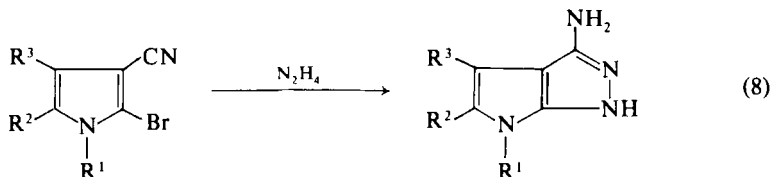
⁸⁴ (a) D. J. Zwanenburg, J. Feijen, and H. Wynberg, *Rec. Trav. Chim. Pays-Bas* **86**, 589 (1967); (b) J. Feijen and H. Wynberg, *ibid.* **89**, 639 (1970).

⁸⁵ (a) R. Kreher and J. Seubert, *Angew. Chem., Int. Ed. Engl.* **3**, 639 (1964); (b) **5**, 967 (1966).

⁸⁶ E. Gonzalez, R. Sarlin, and J. Elguero, *J. Heterocycl. Chem.* **12**, 279 (1975).

⁸⁷ R. L. Tolman and L. B. Townsend, *Tetrahedron Lett.*, 4815 (1968).

ketoesters gave fused pyrroles [Eqs. (10) and (11)].⁹¹ Suitably substituted chloropyrazoles on treatment with thioglycolic acid or 2-mercaptoacetanilide produced fused thiophenes [Eqs. (12)–(14)].



⁸⁸ R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.* **8**, 703 (1971).

⁸⁹ I. Ya. Postovskii and S. V. Sokolov, *Zh. Obshch. Khim.* **29**, 3446 (1959).

⁹⁰ I. Grandberg, S. V. Kabak, N. I. Bobrova, A. N. Kost, and L. G. Vasina, *Khim. Geterotsikl. Soedin.* **1**, 407 (1965); E. Gonzalez, R. Sarlin, and J. Elguero, *Bull. Soc. Chim. Belges*, **85**, 829 (1976).

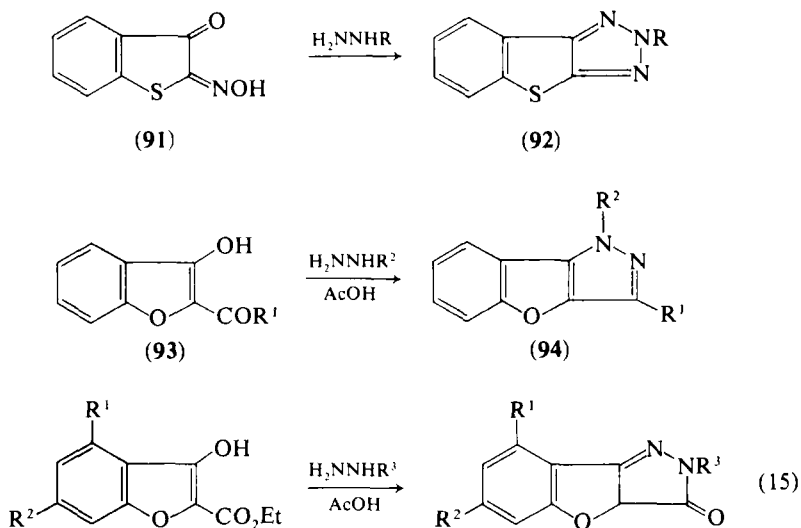
⁹¹ V. I. Shvedov, V. K. Vasil'eva, Yu. I. Trofimkin, and A. N. Grinev, *Khim. Geterotsikl. Soedin.* **9**, 1628 (1973).

⁹² I. Ya. Kvitko, *Khim. Geterotsikl. Soedin.* **5**, 760 (1969).

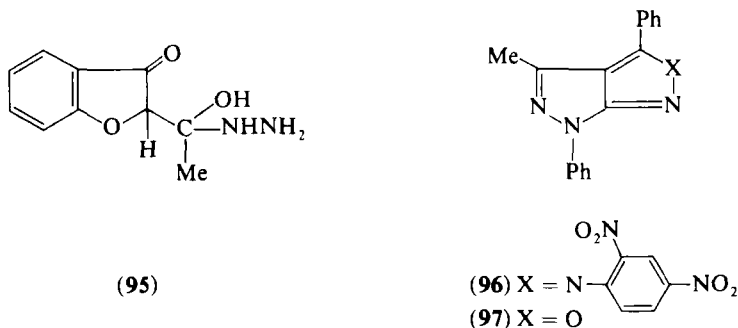
⁹³ I. Ya. Kvitko and T. M. Galkima, *Zh. Org. Khim.* **5**, 1498 (1969).

⁹⁴ Yu. N. Koshelev, I. Ya. Kvitko, and L. S. Efros, *Zh. Org. Khim.* **8**, 1750 (1972).

b. *Condensation of Hydrazines or Hydroxylamine with Heterocyclic Ketones.* Cyclization of hydrazine with heterocyclic ketones has been used for the preparation of benzothieno[2,3-*d*]-*v*-triazoles (**92**),^{97,98} benzothieno[3,2-*c*]pyrazoles (**94**),⁹⁹ and fused pyrazolones [Eq. (15)].¹⁰⁰



The 2-acetyl derivative of benzofuranone (**93**: $R^1 = \text{Me}$) on treatment with hydrazine did not give the expected bicyclic system **94**



⁹⁵ L. N. Zakharov, I. Ya. Kvitko, and A. V. El'tsov, *Zh. Org. Khim.* **9**, 2416 (1973).

⁹⁶ D. H. Kim and A. A. Santilli, U.S. Patent 3,649,641 (1972) [*CA* **76**, 140803 (1972)].

⁹⁷ R. Kirchmayr, German Patent 2,045,795 (1971) [*CA* **75**, 22480 (1971)].

⁹⁸ R. Kirchmayr, U.S. Patent 3,657,266 (1972) [*CA* **77**, 50161 (1972)].

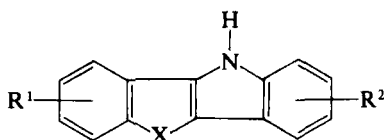
⁹⁹ W. A. Mosher, P. M. Serridge, and D. W. Lipp, *J. Org. Chem.* **37**, 2402 (1972).

¹⁰⁰ W. U. Malik, V. K. Mahesh, and M. Rsisinghani, *Indian J. Chem.* **9**, 655 (1971).

($R^1 = \text{Me}$, $R^2 = \text{H}$); instead, one of three products was isolated, depending on the conditions. At room temperature, a product assigned the structure **95** was obtained, and under reflux conditions the " α -azine" of **93** ($R^1 = \text{Me}$), or 3(2*H*)-benzofuranone hydrazone, were isolated.⁹⁹

4-Benzylidene-3-methyl-1-phenyl-2-pyrazolin-5-one on treatment with 2,4-dinitrophenylhydrazine and hydroxylamine hydrochloride afforded the pyrazolo[3,4-*c*]pyrazole (**96**) and the isoxazolo[3,4-*c*]pyrazole (**97**), respectively.¹⁰¹

c. *Fischer Indole Synthesis*. A number of benzofuro[3,2-*b*]indoles (**98**)^{102–105b} and benzothieno[3,2-*b*]indoles (**99**)^{105a, 106} have been prepared from phenylhydrazines and appropriately substituted 3(2*H*)-benzofuranones and benzothiophenones under normal Fischer indole synthesis conditions.



(**98**) $X = \text{O}$; $R^1 = \text{H}$;
 $R^2 = \text{Me, Br,}^{104} \text{H,}^{102} \text{NO}_2^{104, 105}$

(**99**) $X = \text{S}$; $R^1 = \text{Br, CN, H}$;
 $R^2 = \text{Br, CN, H}$

d. *1,3-Dipolar Cycloaddition Reactions*. Very few compounds have been prepared by this method. Sauter *et al.*^{107, 108} found that benzo-*thiophene* 1,1-dioxides (**100**) underwent addition to diazoalkanes¹⁰⁷ and nitrilimines¹⁰⁸ to give **101** and **102**, respectively. In one case (**102**, $R^1 = \text{H}$, $R^3 = \text{Ph}$), treatment with chloranil in dimethyl formamide (DMF) caused aromatization to the azapentalene **103**.

¹⁰¹ (a) A. M. A. Sammour, M. M. Nonr El-Deen, and M. Abd-El Halim, *J. Chem. UAR* **13**, 7 (1970); (b) A. Sammour, A. Abdel Raouf, M. Elkasaby, and M. A. Hassan, *Egypt. J. Chem.* **15**, 429 (1972).

¹⁰² S. R. Cawley and S. G. P. Plant, *J. Chem. Soc.*, 1214 (1938).

¹⁰³ J. W. Cornforth, G. K. Hughes, F. Lions, and R. H. Harradence, *J. Proc. R. Soc. N.S. Wales* **71**, 486 (1938) [*CA* **33**, 588 (1939)].

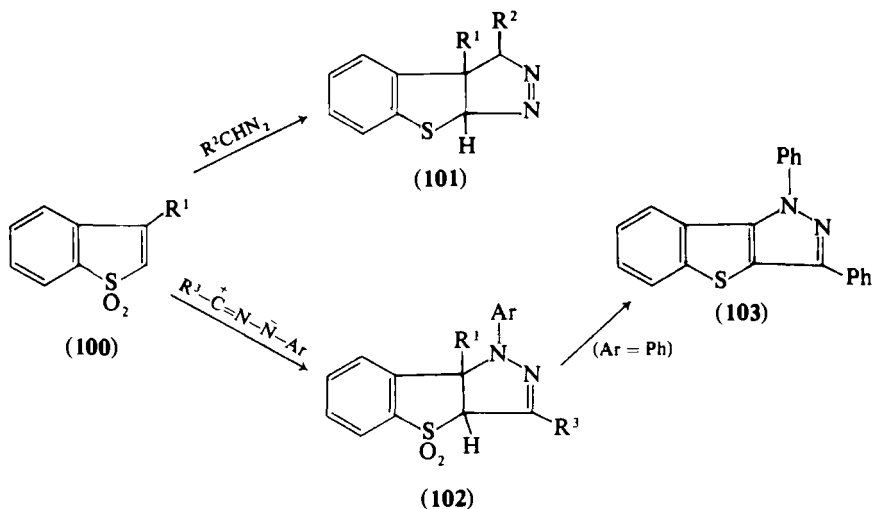
¹⁰⁴ D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.*, 4814 (1956).

¹⁰⁵ (a) D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Mulligan, *J. Org. Chem.* **27**, 586 (1962); (b) L. H. Werner, D. C. Schroeder, and S. Ricca, *J. Am. Chem. Soc.* **79**, 1675 (1957).

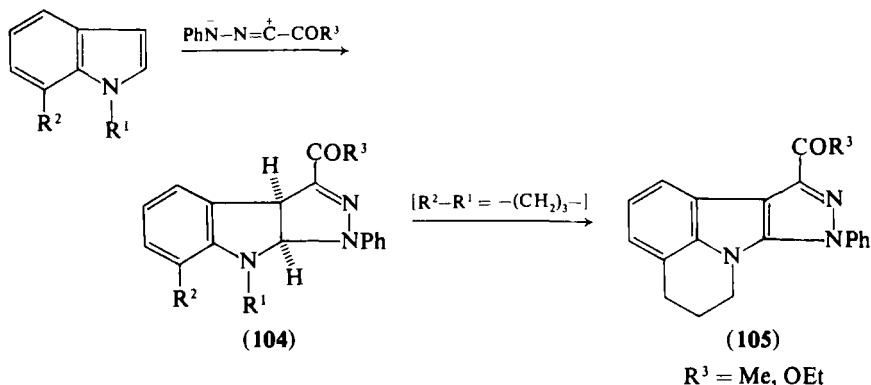
¹⁰⁶ O. Dann, G. Volz, E. Demant, W. Pfeifer, G. Bergen, H. Fick, and E. Walkenhorst, *Justus Liebigs Ann. Chem.*, 1112 (1973).

¹⁰⁷ F. Sauter and G. Büyük, *Monatsh. Chem.* **105**, 550 (1974).

¹⁰⁸ F. Sauter, G. Büyük and U. Jordis, *Monatsh. Chem.* **105**, 869 (1974).



In a similar reaction, Ruccia *et al.*¹⁰⁹ obtained adducts **104** when substituted indoles were treated with nitrilimines. Two of these adducts were readily dehydrogenated with chloranil in xylene to give the pyrazolo[3,4-*b*]indoles (**105**).

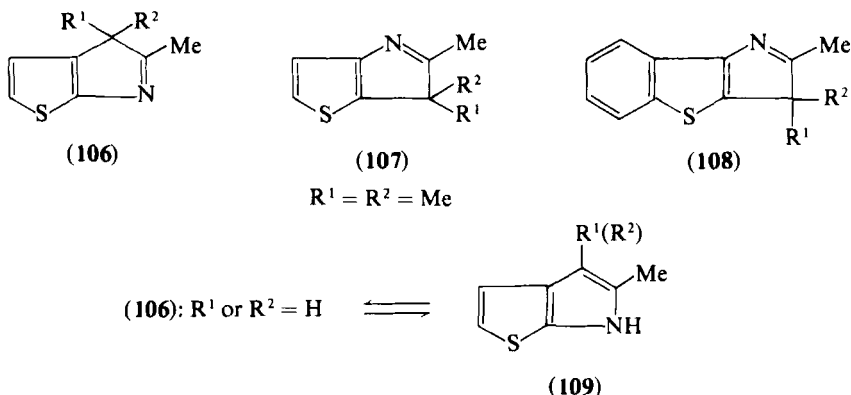


e. *Syntheses from Heterocyclic Amines.* The fused pyrroles **106**, **107**, and **108** have been prepared¹¹⁰ by treatment of the double stannous salt of 2- or 3-aminothiophene, or 3-aminobenzo[*b*]thiophene, respectively, with α -hydroxyisopropyl methyl ketone in the presence of zinc chloride. These syntheses are of interest since preparation of compounds

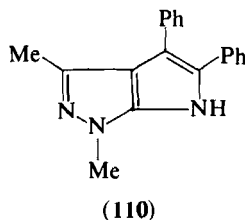
¹⁰⁹ M. Ruccia, N. Vivona, G. Cusmano, M. L. Marino, and F. Piozzi, *Tetrahedron* **29**, 3159 (1973) and references therein.

¹¹⁰ V. G. Zhiryakov and P. I. Abramenko, USSR Patent 166,700 (1964) [*CA* **62**, 10438 (1965)].

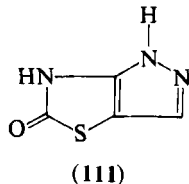
where R^1 or $R^2 = H$ could lead to a tautomeric 10- π -azapentalene system (e.g., **109**).



1,3-Dimethyl-5-aminopyrazole is reported¹¹¹ to undergo acid-catalyzed condensation with benzoin to give the fused pyrazole **110**.



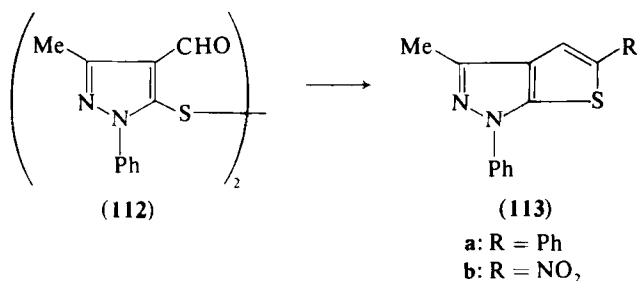
f. Miscellaneous Syntheses. Several systems have been prepared by miscellaneous methods that do not fit into earlier categories. Condensation of 4-amino-2-hydroxythiazole with formylhydrazine gives the pyrazolothiazole **111** in 92% yield.¹¹² Brown and Meth-Cohn¹¹³ obtained the thienopyrazole **113a** by treatment of the pyrazole disulfide **112** with phenylacetic acid and triethylamine. A related compound **113b** was produced from the reaction with nitromethane and triethylamine.



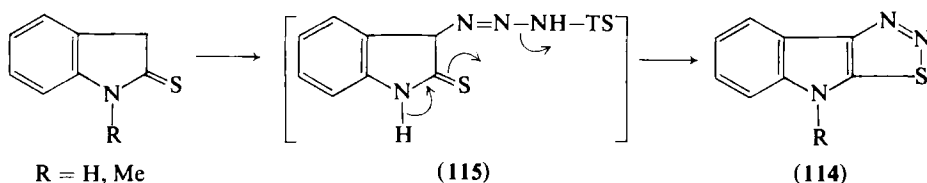
¹¹¹ M. Nakanishi and R. Kobayashi, Japan Kokai 7,375,593 (1973) [*CA* **80**, 146157 (1974)].

¹¹² P. G. Sekachev, *Khim. Geterotsikl. Soedin.* **9**, 1351 (1973).

¹¹³ K. J. Brown and O. Meth-Cohn, *Tetrahedron Lett.*, 4069 (1974).

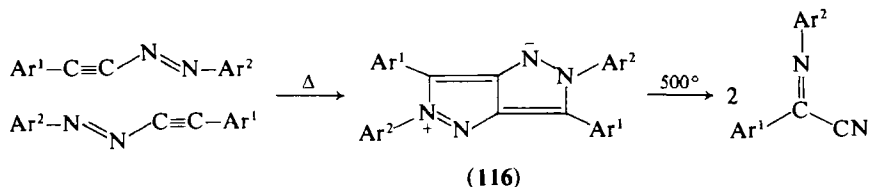


As part of a study of the reactions of arenesulfonyl azides with indoles, Bailey *et al.*¹¹⁴ obtained a compound from the action of tosyl azide on indoline-2-thione to which they ascribed structure **114** (R = H). In contrast, *N*-methylindoline-2-thione gave only a low yield of **114** (R = Me) under the same conditions. Diazo-transfer via an intermediate **115** is thought to be involved; when R = H, facile loss of toluene-*p*-sulfonamide leads to **114a**, but when R = Me, loss of the same fragment leads mainly to other products.



4. Formation of Both Rings Simultaneously

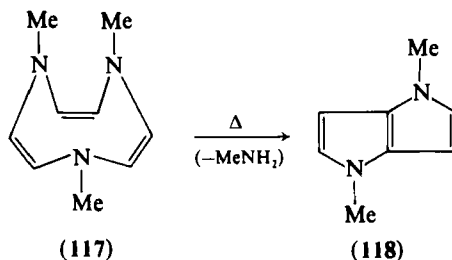
Thermal dimerization of several arylazoethynylarenes in cyclohexane gave mesoionic pyrazolo[4,3-*c*]pyrazoles (**116**) in fair yield. The structure of one product **116** (Ar¹ = Ph; Ar² = *p*-ClC₆H₄) was supported by thermal degradation (500°) to α -(*p*-chlorophenylimino)-phenylacetonitrile and hydrogenation to give two *N*-arylpyrazoles.¹¹⁵



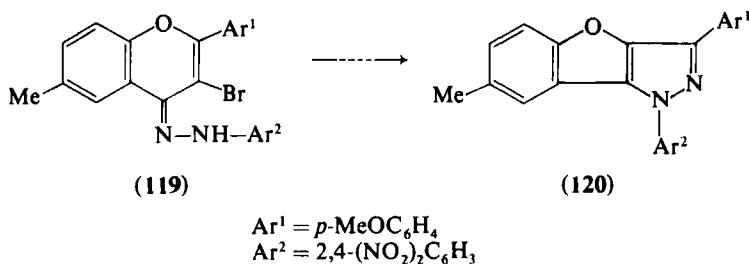
¹¹⁴ A. S. Bailey, J. F. Seager and Z. Rashid, *J. Chem. Soc., Perkin Trans 1*, 2384 (1974).

¹¹⁵ (a) J. H. Lee, A. Matsumoto, O. Simamura, and M. Yoshida, *Chem. Commun.*, 1393 (1969); (b) *Bull. Chem. Soc. Jpn.* **47**, 946 (1974).

The pyrrolo[3,2-*b*]pyrrole (**118**) is reported¹¹⁶ to result from thermolysis of the 12- π -system 1,4,7-trimethyl-1,4,7-triazonine (**117**) in benzene or in the vapor phase. This interesting reaction proceeds with extrusion of methylamine, but the mechanism is uncertain.



Certain flavone hydrazones **119** give the fused system **120** [but the alternative (and more likely) 2-(2,4-dinitrophenyl) structure is not excluded by the evidence presented] on treatment with ethanolic alkali, presumably by initial ring opening of the heterocyclic ring, followed by ring closure with displacement of bromine.¹¹⁷



5. Synthesis by Deprotonation

Several azapentalene anions, **121a**,¹¹⁸ **121b**,¹¹⁹ and **121c**,¹²⁰ have been prepared in solution as their lithium salts by deprotonation of the appropriate dihydro compound with butyllithium in tetrahydrofuran at -10° . The NMR spectra of these compounds suggest that the negative charge is delocalized.²⁰ Reaction with electrophiles leads rapidly to the corresponding dihydro derivatives; thus **121a** gave a monodeutero compound **122** (R = D) with deuterium oxide and a methyl derivative **122** (R = Me) with methyl iodide.

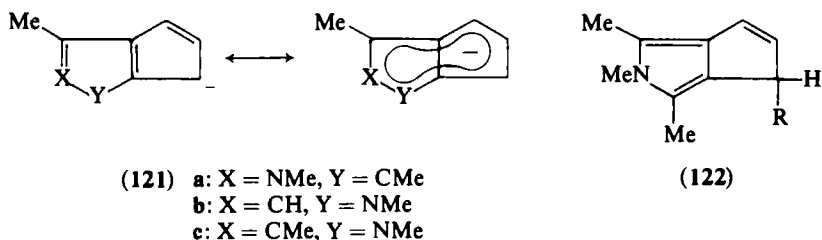
¹¹⁶ H. Prinzbach, R. Schwesinger, M. Breuninger, B. Gallenkamp, and D. Hunkler, *Angew. Chem.* **87**, 349 (1975).

¹¹⁷ K. N. Wadodkar and K. B. Doifode, *Indian J. Chem.* **12**, 224 (1974).

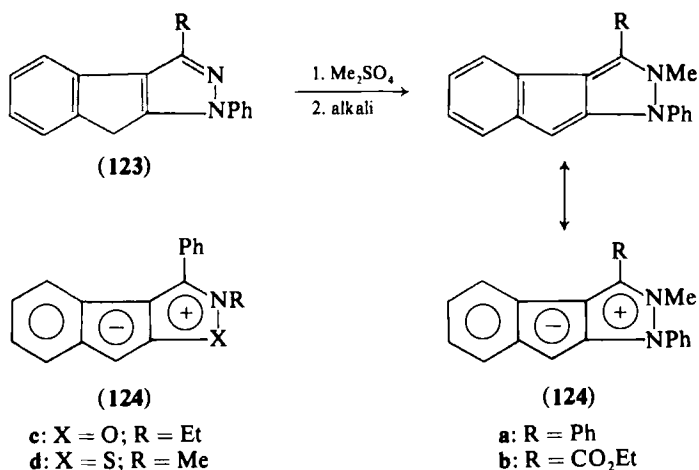
¹¹⁸ H. Volz and B. Messner, *Tetrahedron Lett.*, 4111 (1969).

¹¹⁹ H. Volz, U. Zirngibl, and B. Messner, *Tetrahedron Lett.*, 3593 (1970).

¹²⁰ H. Volz and R. Draese, *Tetrahedron Lett.*, 4917 (1970).



Boyd and Hewson¹²¹ obtained stable, highly colored indeno[2,1-*c*]-pyrazoles (**124a**, **b**) by methylation of the indenopyrazoles (**123**), followed by deprotonation with alkali. These 10- π "pseudoazulenes" react rapidly with electrophiles at C-8 and display a striking bathochromic shift of the long-wavelength absorption band in nonpolar solvents. An attempt to prepare the related indenoisoxazole **124c** failed, though an unstable isothiazole analog (**124d**) could be isolated.¹²²



B. AZAPENTALENES WITH ONE RING JUNCTION NITROGEN ATOM (TYPE B)

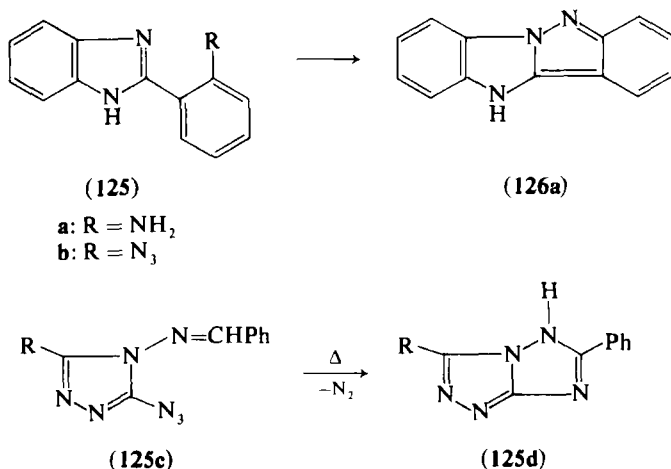
1. [5 + 0] Syntheses

a. *Intramolecular Cyclizations of Nitrene Intermediates.* Like compounds of type A (Section III.A, 1,a), a number of class B azapentalenes have been prepared by cyclization of nitrenes; thus thermal decomposition of the azide **125b** or oxidation of the amino compound **125a**

¹²¹ G. V. Boyd and D. Hewson, *J. Chem. Soc. C*, 2959 (1968).

¹²² G. V. Boyd, *Tetrahedron Lett.*, 1421 (1965).

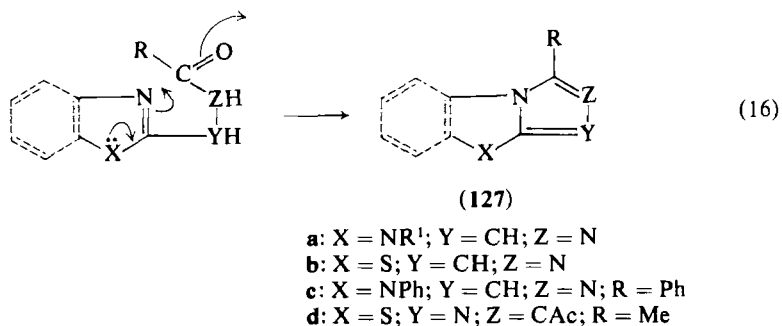
gave the fused benzimidazole **126a**,¹²³ and thermal decomposition of 3-azido-4-benzylideneamino-*s*-triazoles (**125c**) gave *s*-triazolo[3,2-*c*]-*s*-triazoles (**125d**).¹²⁴



b. Intramolecular Cyclization of Amino Groups to Carbon Atoms.

Many systems have been obtained by ring closure between an amine and an electrophilic carbon atom, such as a carbonyl or cyano group. In general, reactions of this type can be divided into two classes, those in which the amino function is a ring nitrogen atom, and those where the amino group is in a side-chain.

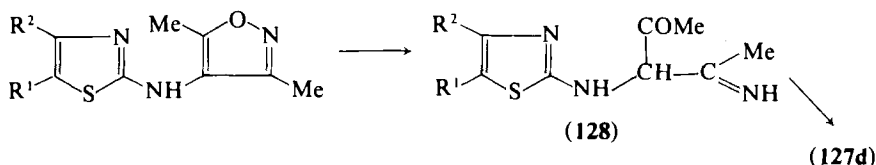
Fused imidazoles, thiazoles, and *s*-triazoles have been prepared by a general method involving intramolecular cyclization of a ring nitrogen atom to a carbonyl group [Eq (16)].



¹²³ (a) H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc. C*, 2289 (1970); (b) 2308 (1970).

¹²⁴ (a) H. H. Takimoto, G. C. Denault, and S. Hotta, *J. Org. Chem.* **30**, 711 (1965); (b) *J. Heterocycl. Chem.* **3**, 119 (1966).

Thus imidazo[1,5-*a*]benzimidazoles (**127a**)¹²⁵⁻¹²⁷ were obtained from 2-acylaminomethylbenzimidazoles with phosphorus oxychloride, and imidazo[5,1-*b*]thiazoles, and benzothiazoles (**127b**)¹²⁸ were obtained from the corresponding 2-acylaminomethyl derivatives under the same conditions. Pyrazolo[3,2-*c*]-*s*-triazoles were prepared in Kodak Laboratories¹²⁹ by an analogous procedure. Imidazo[1,5-*b*]-*s*-triazoles (**127c**)^{130a} were produced from a similar intermediate with polyphosphate ester (PPE), and 6-acetylimidazo[2,1-*b*]thiazoles (**127d**) from an intermediate **128** resulting from the hydrogenolysis of an isoxazole derivative.^{130b}



In the same way, pyrrolo[1,2-*a*]benzimidazoles (**129**) resulted from thermal cyclization of 2-substituted benzimidazoles according to Eq. (16)^{130c} and a series of fused isoindoles **130**, prepared according to Eq. (17), feature in a number of patents.^{131, 132} 2,3-Benzo analogs of **130** have also been obtained by the same route.¹³³

¹²⁵ V. M. Aryuzina and M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **6**, 525 (1970).

¹²⁶ (a) V. M. Aryuzina and M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **2**, 605 (1966); (b) **4**, 506 (1968); (c) **4**, 509 (1968); (d) **4**, 1108 (1968).

¹²⁷ (a) V. M. Aryuzina and M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **8**, 396 (1972); (b) **9**, 395 (1973).

¹²⁸ (a) T. Pyl, O. Sietz and K. Staeger, *Justus Liebigs Ann. Chem.* **679**, 144 (1964); (b) V. V. Avidon and M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **1**, 64 (1965); (c) **1**, 349 (1965); (d) **4**, 719 (1968).

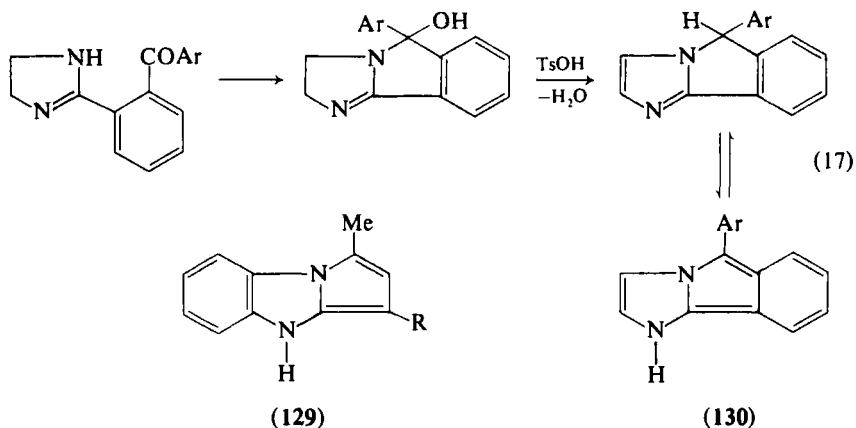
¹²⁹ (a) J. Bailey, E. B. Knott, and P. A. Marr (Kodak Ltd.), British Patent 1,253,933 (1971) [*CA* **76**, 87186 (1972)]; (b) German Patent 1,810,462 (1971); [*CA* **76**, 47395 (1972)]; (c) British Patent 1,252,418 (1971).

¹³⁰ (a) K. Meguro and Y. Kuwada, *Heterocycles* **2**, 335 (1974); (b) V. Sprio, O. Migliara, and E. Ajello, *J. Heterocycl. Chem.* **11**, 91 (1974); (c) Z. V. Esayan, L. A. Manucharova, and G. T. Tatevosyan, *Arm. Khim. Zh.* **25**, 345 (1972) [*CA* **77**, 139889 (1972)].

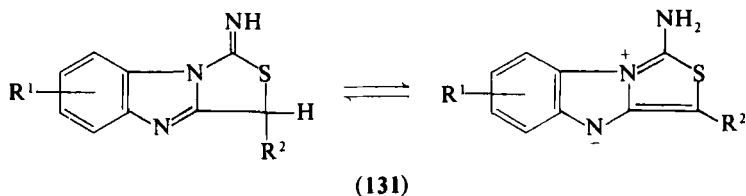
¹³¹ W. J. Houlihan (Sandoz Inc.), U.S. Patent 3,403,164 (1968) [*CA* **70**, 37810 (1969)]; German Patent 1,814,540 (1969) [*CA* **71**, 81368 (1969)]; German Patent 1,901,497 (1969) [*CA* **71**, 112934 (1969)]; W. J. Houlihan and M. K. Eberle (Sandoz Ltd.), German Patent 1,930,488 (1970) [*CA* **72**, 121532 (1970)]; W. J. Houlihan and G. A. Cook (Sandoz Ltd.), German Patent 2,023,633 (1970) [*CA* **74**, 42360 (1971)]; W. J. Houlihan (Sandoz Ltd.), British Patent 1,225,411 (1971) [*CA* **75**, 63790 (1971)]; British Patent 1,225,413 (1971) [*CA* **75**, 36040 (1971)]; British Patent 1,232,469 (1971) [*CA* **75**, 63788 (1971)]; French Patent 2,034,663 (1971) [*CA* **75**, 76793 (1971)]; Swiss Patent 499,529 (1971) [*CA* **75**, 20404 (1971)].

¹³² M. Chaykovsky, L. Benjamin, R. Ian Fryer, and W. Metlesics, *J. Org. Chem.* **35**, 1178 (1970).

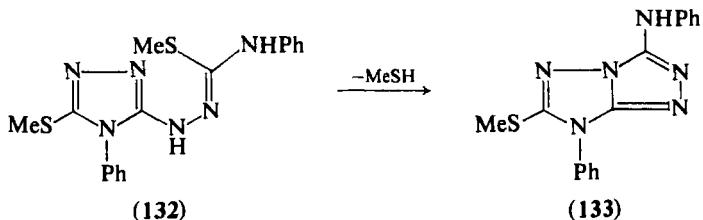
¹³³ M. K. Eberle, W. J. Houlihan, and P. Schirm, *J. Org. Chem.* **38**, 3872 (1973).



Cyclization between a ring nitrogen atom and the cyano group in 2-thiocyanatoalkylbenzimidazoles on heating yielded stable 1-iminothiazolo[3,4-*a*]benzimidazoles (**131**) which can be written as a 1,3-dipolar tautomer possessing a 14- π -electron system.¹³⁴ The chemical reactivity of **131** has been investigated.^{134b}



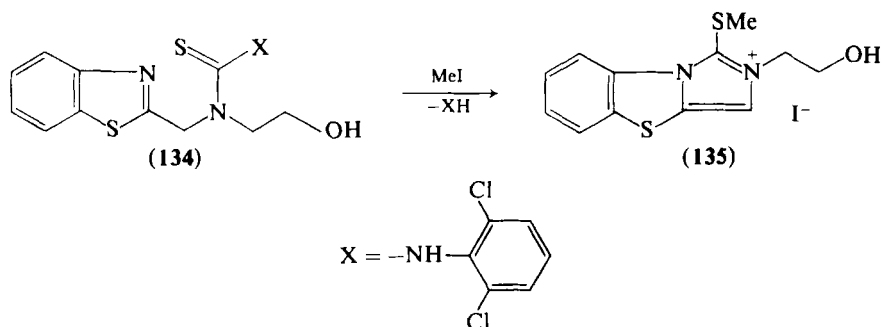
Loss of methanethiol from **132** following nucleophilic attack by a ring nitrogen atom under basic conditions, or thermally, afforded the *s*-triazolo[4,3-*b*]-*s*-triazole (**133**).¹³⁵ In a recently reported reaction,¹³⁶ methylation of the thioamide group in **134** resulted in cyclodeamination to give the quaternary salt **135** with loss of 2,6-dichloroaniline, rather than loss of methanethiol as in **132** \rightarrow **133**.



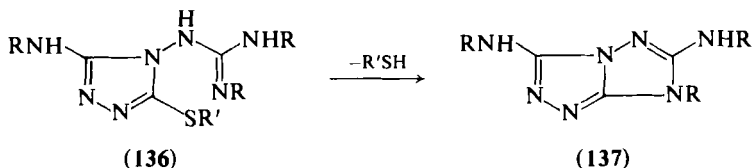
¹³⁴ (a) R. D. Haugwitz, B. V. Maurer, and V. L. Narayanan, *Chem. Commun.*, 1100 (1971); (b) *J. Org. Chem.* **39**, 1359 (1974).

¹³⁵ A. Dornow and H. Paucksh, *Chem. Ber.* **99**, 85 (1966).

¹³⁶ J. Ashby and D. Griffiths, *Synthesis*, 511 (1975).



Examples of syntheses in which the heterocyclic ring is generated by cyclization of an exocyclic amine to an electrophilic carbon atom include the preparation of triazolo[4,3-*b*]triazoles (**137**) by elimination of alkanethiol from guanidine derivatives **136**¹³⁷ (cf. **132** → **133**), and many examples (mostly in patents) of pyrazolo[1,5-*a*]benzimidazoles prepared according to Eq. (18).^{138–142}



¹³⁷ F. Kurzer and M. Wilkinson, *J. Chem. Soc. C*, 2099 (1968).

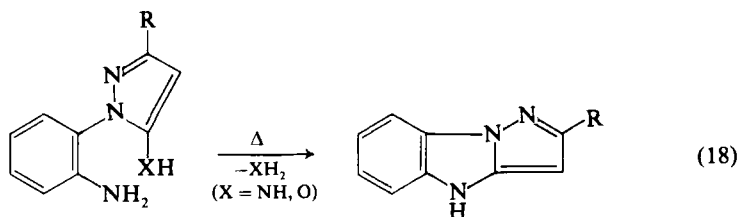
¹³⁸ (a) K. H. Menzel, O. Wahl, and W. Peiz (Agfa A.-G.), Belgium Patent 579,898 (1959); German Patent 1,070,030 (1959).

¹³⁹ (a) O. Wahl and K. H. Menzel (Agfa A.-G.), German Patent 1,099,349 (1961) [*CA* **56**, 10333 (1962)]; (b) K. Loeffler and K. H. Menzel (Agfa A.-G.), Belgium Patent 621,241 (1962) [*CA* **59**, 7534 (1963)]; (c) G. Schaum and K. H. Menzel (Agfa A.-G.), German Patent 1,158,836 (1963) [*CA* **60**, 6388 (1964)]; (d) K. H. Menzel and W. Pueschel, *Mitt. Forschungslab. AGFA-Gevaert AG Leverkusen—Muenchen* **4**, 376 (1964) [*CA* **64**, 3734 (1966)]; (e) K. H. Menzel and R. Puetter (Agfa A.-G.), Belgium Patent 643,802 (1964) [*CA* **63**, 4441 (1965)]; (f) K. H. Menzel (Agfa A.-G.), Belgium Patent 658,107 (1965) [*CA* **64**, 8362 (1966)].

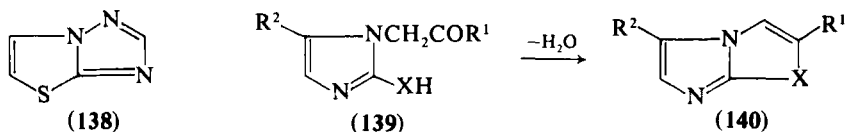
¹⁴⁰ (a) Konishiroku Photo Industry Co., Ltd., British Patent 1,241,069 (1971) [*CA* **76**, 87183 (1972)]; (b) Japanese Patent 7,110,068 (1971) [*CA* **75**, 22490 (1971)].

¹⁴¹ (a) W. Scholl and G. Dittmar (Bayer A.-G.), Belgium Patent 626,394 (1963) [*CA* **60**, 13360 (1964)]; (b) H. Raab (Bayer A.-G.), Belgium Patent 635,490 (1963) [*CA* **61**, 14829 (1964)]; (c) Bayer A.-G., British Patent 927,614 (1963) [*CA* **62**, 2854 (1965)]; (d) H. Wunderlich and K. H. Menzel (Bayer A.-G.), Belgium Patent 642,347 (1964) [*CA* **63**, 4428 (1965)]; (e) K. H. Menzel, W. Wirth, and H. Kreiskott (Bayer A.-G.), German Patent 1,178,075 (1964) [*CA* **61**, 14682 (1964)]; (f) Bayer A.-G., British Patent 951,113 (1964) [*CA* **62**, 6599 (1965)]; (g) Bayer A.-G., French Patent M 3709 (1966) [*CA* **66**, 79557 (1967)]; (h) G. Wolfrum, R. Puetter, and K. Menzel (Bayer A.-G.), German Patent 1,234,891 (1967) [*CA* **66**, 105886 (1967)].

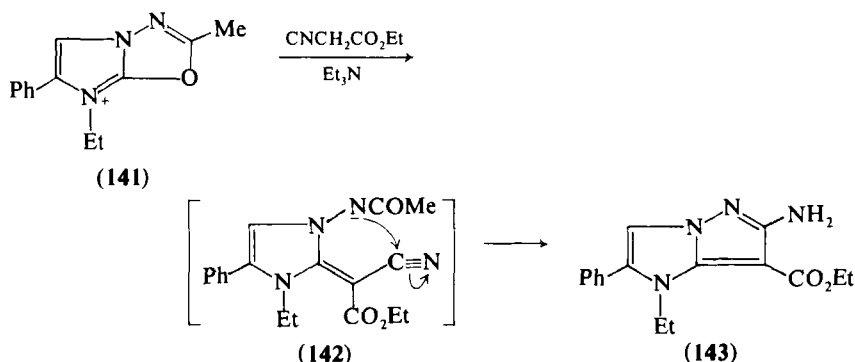
¹⁴² S. Mignonac-Mondon, J. Elguero, and R. Lazaro, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **276**, 1533 (1973).



Acidic cyclodehydration of 3-amino-2-formamidothiazolium mesylate to give **138**¹⁴³ and preparation of imidazo[1,2-*a*]imidazoles (**140**: X = NH)¹⁴⁴ and imidazo[2,1-*b*]thiazoles (**140**: X = S)¹⁴⁵ by dehydrative cyclization of the corresponding imidazoles (**139**: X = NH, S) are examples of syntheses by cyclization of exocyclic amines to carbonyl groups.



On treatment with ethyl cyanoacetate and base, the fused 1,3,4-oxadiazolium salt **141** underwent ring opening with subsequent closure to the fused pyrazole **143** in low yield, probably via the intermediate **142**.¹⁴⁶ This reaction proceeds by analogy with the reactions of monocyclic oxadiazolium salts,¹⁴⁷ but a similar intermediate **145** obtained from the fused thiadiazolium salt **144** failed to cyclize to a bicyclic system under a variety of conditions.¹⁴⁶



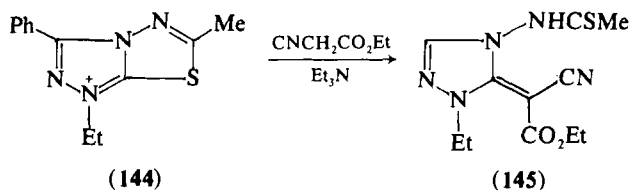
¹⁴³ (a) Y. Tamura, H. Hayashi, J. H. Kim and M. Ikeda, *J. Heterocycl. Chem.* **10**, 947 (1973); (b) Y. Tamura, H. Hayashi, E. Saeki, J. H. Kim, and M. Ikeda, *ibid.* **11**, 459 (1974).

¹⁴⁴ A. Lawson, *J. Chem. Soc.*, 307 (1956).

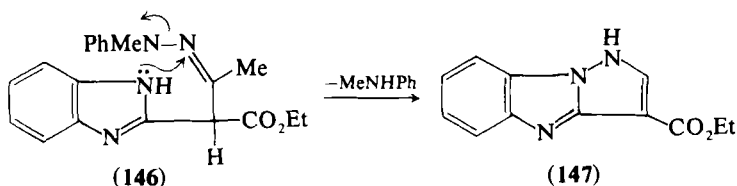
¹⁴⁵ A. Lawson and H. V. Morley, *J. Chem. Soc.*, 566 (1957).

¹⁴⁶ (a) J. Elguero, R. Jacquier, and A. J. H. Summers, *Bull. Soc. Chim. Fr.*, 3968 (1972); (b) A. Ya. Lazaris, S. M. Shmulovich, and A. N. Egorochkin, *Zh. Org. Khim.* **10**, 2236 (1974).

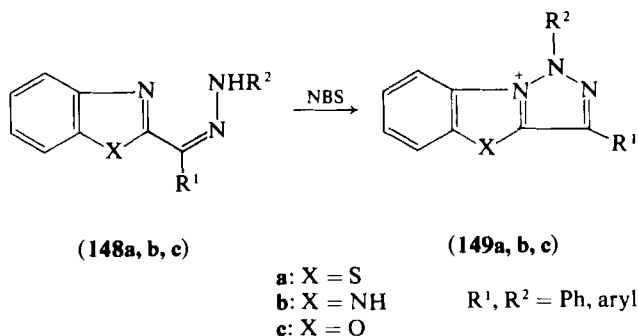
¹⁴⁷ G. V. Boyd and S. R. Dando, *J. Chem. Soc. C*, 225 (1971).



c. *Intramolecular Cyclization of Nitrogen Atoms.* Displacement of methylaniline from the methylphenylhydrazone (146) was found to occur on treatment with acid to give the pyrazolo[1,5-*a*]benzimidazole (147).¹⁴⁸



Messmer and Gelléri¹⁴⁹ found that cyclization of arylhydrazones 148 occurred with *N*-bromosuccinimide at room temperature to give the fused benzothiazolium 149a and benzimidazolium 149b salts. When the analogous benzoxazole phenylhydrazone (148c: R² = Ph) was used, cyclization did not take place and the starting material was recovered. Compound 149b gave the free base on deprotonation with pyridine.

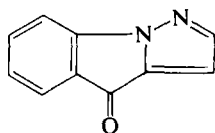


d. *Friedel-Crafts and Related Reactions.* A few compounds have been prepared by this method. The pyrazolo[1,5-*a*]indole (150) was obtained from 1-phenylpyrazole-5-carboxylic acid with polyphosphoric

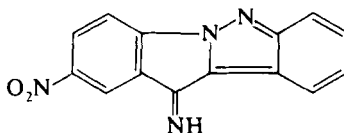
¹⁴⁸ D. Das Gupta and T. Nath Gosh, *Sci. Culture* **4**, 739 (1939).

¹⁴⁹ A. Messmer and A. Gelléri, *Angew. Chem. Int. Ed. Engl.* **6**, 261 (1967).

acid,¹⁵⁰ and the indolo[1,2-*b*]indazole (**151**) was formed by cyclization of 2-(indazol-2'-yl)-5-nitrobenzonitrile under acidic conditions.¹⁵¹

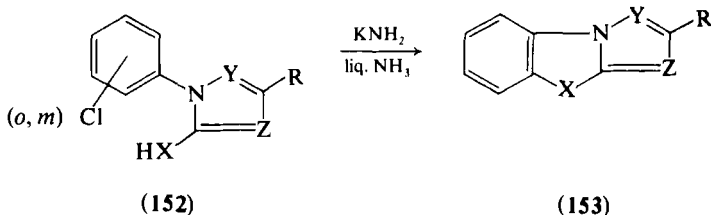


(150)



(151)

e. Intramolecular Cyclization of Other Intermediates. Various systems possessing an annelated benzene ring have been obtained by cyclization of benzyne intermediates. Potassium amide in liquid ammonia was used to generate a benzyne intermediate from the *N*-(*o*-chlorophenyl)pyrazole (**152a**), which cyclized to 2-methylpyrazolo[1,5-*a*]benzimidazole (**153a**) in good yield.¹⁴² The same conditions were successfully used to synthesize imidazo[2,1-*b*]benzothiazoles^{152a} (**153b**) and imidazo[2,1-*b*]benzoxazoles^{152b} (**153c**) from 1-(*m*-chlorophenyl)-2-mercaptoimidazole (**152b**) and 1-(*o*-chlorophenyl)-2-hydroxyimidazoles (**152c**), respectively.



(152)

(153)

- a: X = NH; Y = N; Z = CH; R = Me
 b: X = S; Y = CH; Z = N; R = H
 c: X = O; Y = CH; Z = N; R = H

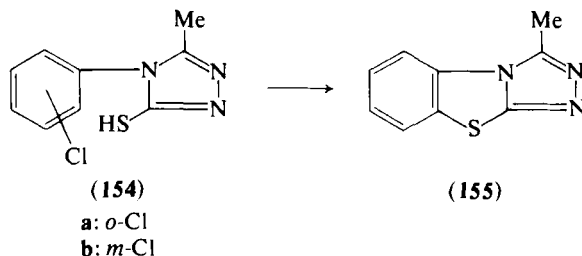
Wikel and Paget¹⁵³ showed that a benzyne intermediate was not participating in the cyclization of **154a** to the fused benzothiazole **155** with sodium hydride since the isomeric chloro compound **154b** did not give **155** either under the same conditions or on treatment with potassium amide in liquid ammonia.

¹⁵⁰ (a) D. A. Shirley and P. W. Alley, *J. Am. Chem. Soc.* **79**, 4922 (1957); (b) **80**, 6271 (1958).

¹⁵¹ D. J. Gale and J. F. K. Wilshire, *Aust. J. Chem.* **26**, 2683 (1973).

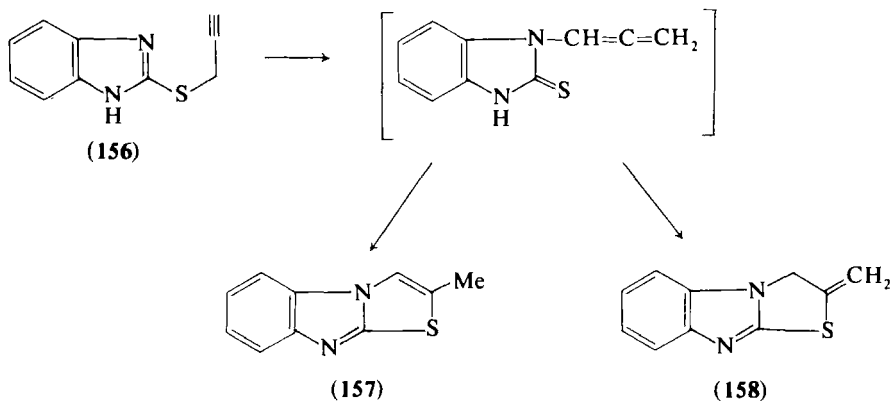
¹⁵² (a) H. Ogura and T. Itoh, *Chem. Pharm. Bull.* **18**, 1981 (1970); (b) H. Ogura, T. Itoh and S. Sugimoto, *ibid.* **18**, 2204 (1970).

¹⁵³ J. H. Wikel and C. J. Paget, *J. Org. Chem.* **39**, 3506 (1974).



Reaction of several *o*- and *m*-substituted chlorophenylpyrazole and imidazole derivatives with potassium amide in liquid ammonia did not form the aryne intermediate that might have led to 3a-azapentalene systems.¹⁵⁴

f. *Rearrangements.* A variety of rearrangements, ring-contraction and ring-expansion reactions, have been shown to produce specific azapentalenes. Balasubramanian and Venugopalan¹⁵⁵ found that 2-propargylthiobenzimidazole (156) underwent a Claisen-type 3,3-sigmatropic rearrangement to the thiazolo[3,2-*a*]benzimidazole (157) and its exomethylene isomer 158 in good yield on heating in hexamethylphosphotriamide (HMPT).



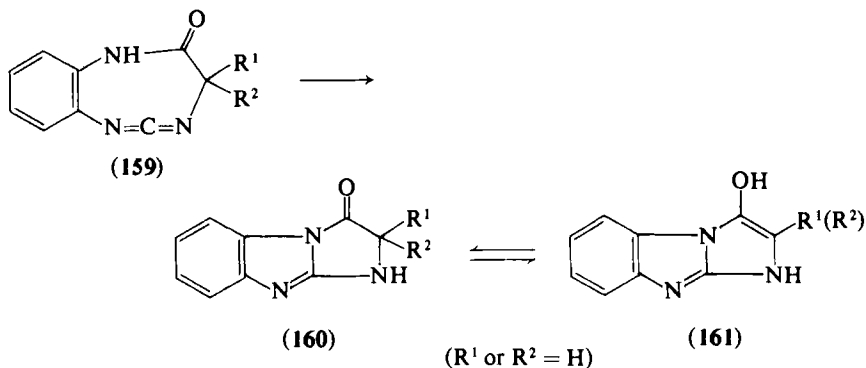
Transposition reactions of larger ring systems sometimes produce azapentalenes. Of these, the formation of pyrrolo[1,2-*a*]imidazoles from 1,4-diazocines is probably the most important, and this is discussed below (Sections III,B,4,a and IV,B,2).

Intramolecular cyclization of the cyclic carbodiimide 159 provides an interesting route to the imidazo[1,2-*a*]benzimidazole (160: $R^1 = R^2 =$

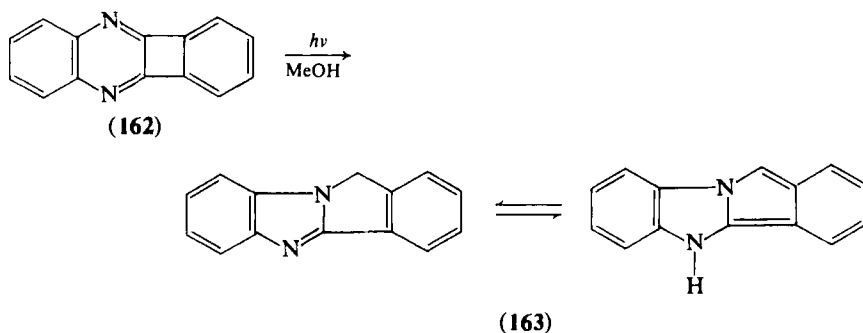
¹⁵⁴ R. M. Claramunt, R. Granados, and M. C. Repollés, *An. Quim.* **71**, 206 (1975).

¹⁵⁵ K. K. Balasubramanian and B. Venugopalan, *Tetrahedron Lett.*, 2643 (1974).

Ph).¹⁵⁶ A modification of this method using a system where R¹ or R² was H could lead to an aromatic system **161**.



Isoindolo[2,1-*a*]benzimidazole (**163**) was the sole product produced (80% yield) on irradiation of the quinoxaline derivative **162** in methanol.¹⁵⁷ The authors propose a mechanism that involves initial ring-opening of **162** to a diazocine biradical that undergoes transposition and reduction to the azapentalene **163**.

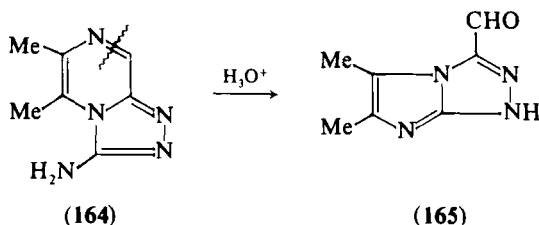


Ring contractions of six- or seven-membered fused systems have sometimes been used to synthesize azapentalenes. Taylor *et al.*¹⁵⁸ found that triazolo[4,3-*a*]pyrazines (**164**) rearrange in acid to imidazotriazoles **165** following initial fission of the six-membered ring at the point shown (**164**). The kinetics^{158b} of this reaction have revealed the intermediacy of covalently hydrated species.

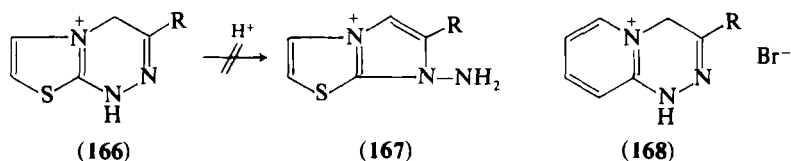
¹⁵⁶ C. W. Bird, M. W. Kaczmar and C. K. Wong, *Tetrahedron* **30**, 2549 (1974).

¹⁵⁷ J. I. Sarkisian and R. W. Binkley, *J. Org. Chem.* **35**, 1228 (1970).

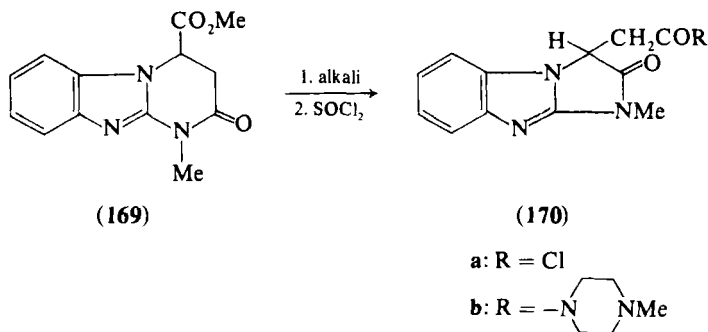
¹⁵⁸ (a) F. L. Rose, G. J. Stacey, P. J. Taylor, and T. W. Thompson, *Chem. Commun.*, 1524 (1970); (b) S. Nicholson, G. J. Stacey, and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 4 (1972).



It was hoped that ring contraction of the triazinium salt **166** would give imidazo[2,1-*b*]thiazolium salts (**167**) on treatment with acid, but instead the free base of **166** was isolated on work-up of the reaction.¹⁵⁹ Related pyridotriazine hydrobromides **168** underwent contraction in acid to give imidazopyridinium salts.



Troxler and Weber¹⁶⁰ found that alkali cleaved the dihydropyrimidine ring in **169** to a diacid that cyclized to the imidazobenzimidazole **170a** with thionyl chloride. Subsequent treatment with methylpiperazine yielded a stable derivative **170b**.

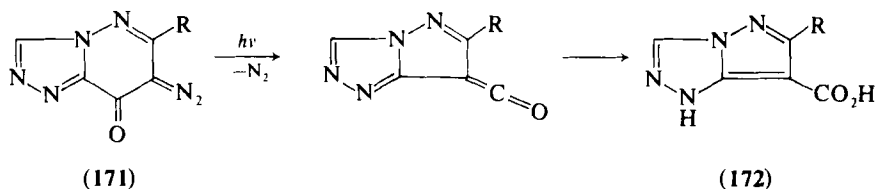


Photolysis of the diazocompound **171** caused ring contraction to the pyrazolo[3,2-*c*]-s-triazole (**172**) via rearrangement of the first-formed α -ketocarbene and hydrolysis of an intermediate ketene.¹⁶¹

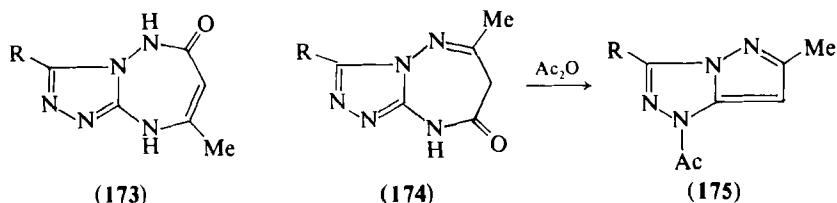
¹⁵⁹ E. E. Glover and K. D. Vaughan, *J. Chem. Soc., Perkin Trans. 1*, 1137 (1974).

¹⁶⁰ F. Troxler and H. P. Weber, *Helv. Chim. Acta* **57**, 2356 (1974).

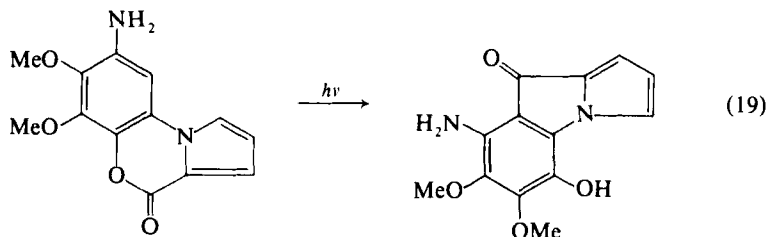
¹⁶¹ (a) H.G.O. Becker and H. Böttcher, *J. Prakt. Chem.* **314**, 55 (1972); (b) H. G. O. Becker, D. Nagel, and H. J. Timpe, *Z. Chem.* **13**, 213 (1973).



Rearrangement of triazolotriazepinones **174** (prepared by the action of ethyl acetoacetate on 4,5-diamino-*s*-triazoles) has been shown to take place in acetic anhydride to give pyrazolo[3,2-*c*]-*s*-triazoles (**175**).¹⁶² The mechanism of this reaction is being investigated.¹⁶³ It has been conclusively shown that compounds of structure **174** (not **173** as previously thought¹⁶⁴) result from the action of ethyl acetoacetate on 3-substituted 4,5-diamino-*s*-triazoles.¹⁶²



Other ring contractions that give azapentalene derivatives include the rearrangement of a fused oxazine to a pyrazolo[1,5-*a*]indol-4-one with acetic anhydride,¹⁶⁵ and an interesting photochemical contraction of a cyclic lactone, which produces an isomeric fused indolone by a mechanism thought to involve the first *meta* photo-Fries rearrangement [Eq. (19)].¹⁶⁶ The product was used as an intermediate for the synthesis of mitomycin antibiotics (Section VI,A).



¹⁶² (a) R. M. Claramunt, J. M. Fabrega, and J. Elguero, *J. Heterocycl. Chem.* **11**, 751 (1974); (b) F. Leroy, J. Housty, S. Geoffre, and M. Hospital, *Cryst. Struct. Commun.* **4**, 317 (1975).

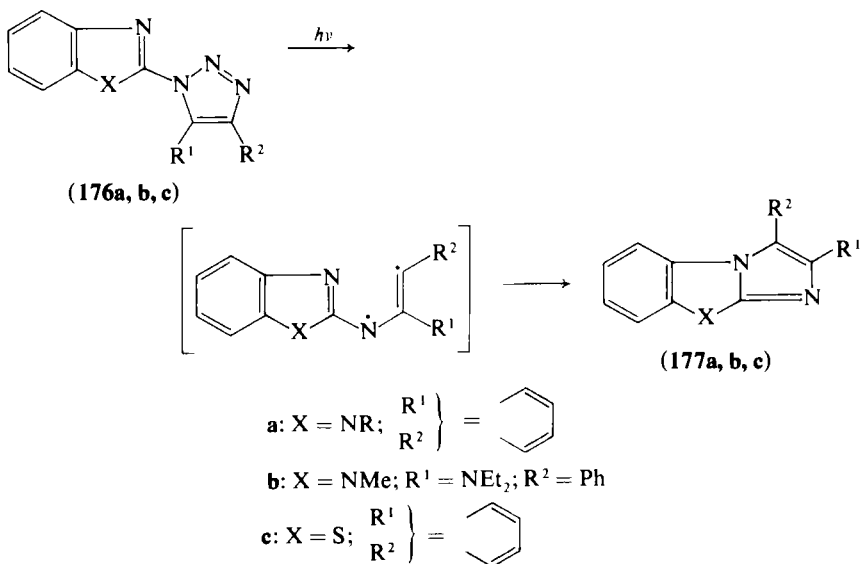
¹⁶³ (a) E. M. Essassi, J. P. Laverigne, P. Viallefont, and J. Daunis, *J. Heterocycl. Chem.* **12**, 661 (1975); (b) P. Viallefont, unpublished results.

¹⁶⁴ H. Gehlen and R. Drohla, *Arch. Pharm.* **303**, 709 (1970).

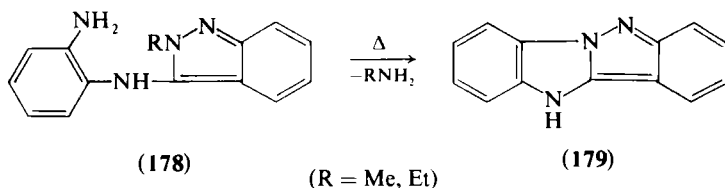
¹⁶⁵ R. Hunt, S. T. Reid, and K. T. Taylor, *Tetrahedron Lett.*, 2861 (1972).

¹⁶⁶ G. J. Siuta, R. W. Franck, and A. A. Ozorio, *Chem. Commun.*, 910 (1974).

g. *Miscellaneous Syntheses.* Irradiation of 2-benzotriazolyl-benzimidazole (**176a**) resulted in loss of nitrogen from the triazole ring and cyclization of the biradical intermediate to give **177a**.¹⁶⁷ In the same way, thermal extrusion of nitrogen from **176b** afforded the imidazo-benzimidazole **177b** in 20% yield,¹⁶⁸ and photochemical or thermal elimination of nitrogen from **176c** gave benzimidazo[2,1-*b*]benzothiazole (**177c**).^{169a} This last compound has also been prepared by thermal cyclization (950°) of 1-phenylbenzimidazole-2-thione.^{169b}



N-Methyl- and *N*-ethylindazoles **178** slowly cyclize to benzimidazo-[1,2-*b*]indazole (**179**) on prolonged boiling in ethylene glycol.^{123a}

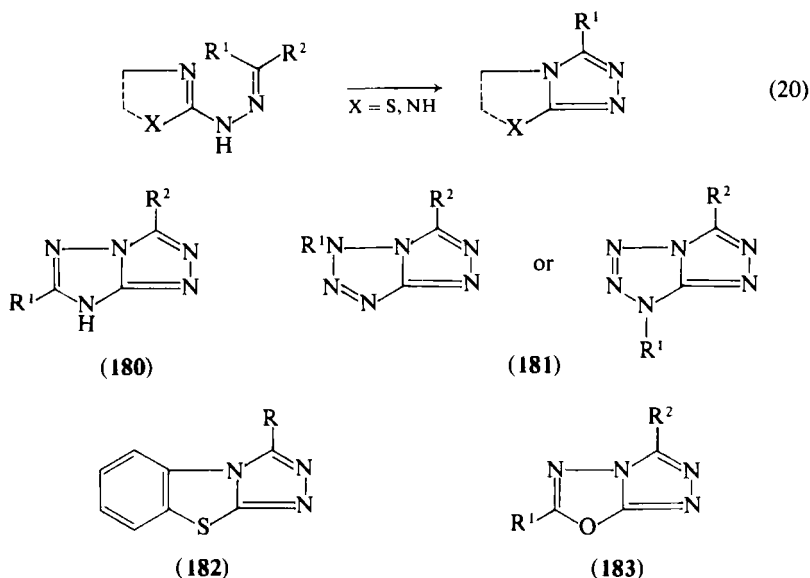


¹⁶⁷ (a) A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 2828 (1970); (b) J. de Mendoza and J. Elguero, *Bull. Soc. Chim. Fr.*, 2987 (1974).

¹⁶⁸ Y. Shiokawa and S. Ohki, *Chem. Pharm. Bull.* **21**, 981 (1973).

¹⁶⁹ (a) D. C. K. Lin and D. C. De Jongh, *J. Org. Chem.* **39**, 1780 (1974); (b) D. C. K. Lin, M. L. Thomson, and D. C. De Jongh, *Can. J. Chem.* **53**, 2293 (1975).

Scott and others have shown that the hydrazones of many azoles undergo ring closure to fused triazoles [Eq. 20] either by oxidation ($R^2 = H$) or by displacement of halogen ($R^2 = Br$). Thus triazolotriazoles (180) were obtained by lead tetraacetate oxidation of the corresponding *s*-triazolehydrazone,¹⁷⁰⁻¹⁷² or by displacement of bromine¹⁷³ from the appropriate bromo derivative. *s*-Triazolo[4,3-*d*]tetrazoles (181) were prepared by oxidation^{172, 174, 175} or displacement of bromine¹⁷⁵⁻¹⁷⁹ from the appropriate derivative, and similar methods were used to prepare *s*-triazolobenzothiazoles^{172, 180, 181} (182) *s*-triazolooxadiazoles (183),^{172, 182, 183} and pyrazolo[3,2-*c*]-*s*-triazoles.¹²⁹



¹⁷⁰ H. Gehlen and F. Lemme, *Justus Liebigs Ann. Chem.* **703**, 116 (1967).

¹⁷¹ F. L. Scott and T. A. F. O'Mahony, *Tetrahedron Lett.*, 1841 (1970).

¹⁷² R. N. Butler, F. L. Scott, and T. A. F. O'Mahony, *Chem. Rev.* **73**, 93 (1973).

¹⁷³ F. L. Scott and J. B. Aylward, *Tetrahedron Lett.*, 841 (1965).

¹⁷⁴ F. L. Scott and R. N. Butler, *J. Chem. Soc. C*, 1202 (1966).

¹⁷⁵ R. N. Butler and F. L. Scott, *J. Chem. Soc. C*, 1711 (1968).

¹⁷⁶ F. L. Scott, R. N. Butler, and D. A. Cronin, *Angew. Chem., Int. Ed. Engl* **4**, 950 (1965).

¹⁷⁷ R. N. Butler and F. L. Scott, *J. Chem. Soc. C*, 239 (1967).

¹⁷⁸ J. C. Tobin, A. F. Hegarty, and F. L. Scott, *J. Chem. Soc. B*, 2198 (1971).

¹⁷⁹ F. L. Scott, D. A. Cronin, and J. K. O'Halloran, *J. Chem. Soc. C*, 2769 (1971).

¹⁸⁰ R. N. Butler, P. O'Sullivan, and F. L. Scott, *J. Chem. Soc. C*, 2265 (1971).

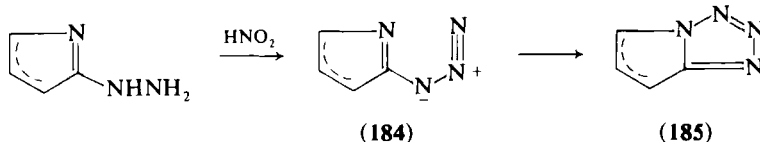
¹⁸¹ R. N. Butler, P. O'Sullivan, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1519 (1972).

¹⁸² F. L. Scott, T. M. Lambe, and R. N. Butler, *Tetrahedron Lett.*, 1729 (1971).

¹⁸³ R. N. Butler, T. M. Lambe, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 1*, 269 (1972).

2. [4 + 1] Syntheses

a. *Introduction of a Nitrogen Atom.* The reaction of heterocyclic hydrazines with nitrous acid to give azides **184** or tetrazoles **185** (Scheme 6) constitutes a general route to azapentalenes with a tetrazole ring. Table I lists the systems prepared in this way. The question of tetrazole = azide isomerism is discussed in Section IV,B,1.



SCHEME 6

TABLE I: FUSED TETRAZOLES PREPARED ACCORDING TO SCHEME 6

System	References	Compound No.
Tetrazolo[5,1- <i>a</i>]isoindoles	184, 332	186a
Thiazolo[3,2- <i>d</i>]tetrazoles	185	187a
Tetrazolo[1,5- <i>a</i>]benzimidazoles	185, 186	186b
Pyrazolo[1,5- <i>d</i>]tetrazoles	187	188
Tetrazolo[5,1- <i>b</i>]benzothiazoles	185, 189	186c
Tetrazolo[5,1- <i>b</i>]benzoxazoles	185	186d
Tetrazolo[5,1- <i>b</i>]naphtho[1',2'- <i>d</i>]thiazoles	188a	189
Tetrazolo[5,1- <i>b</i>]naphtho[2',1'- <i>d</i>]thiazoles	188	190
<i>s</i> -Triazolo[2,3- <i>d</i>]tetrazoles	190	187b
Tetrazolo[5,1- <i>d</i>]tetrazoles	191	187c

¹⁸⁴ M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970).

¹⁸⁵ (a) G. A. Reynolds, J. A. Van Allan, and J. F. Tinker, *J. Org. Chem.* **24**, 1205 (1959); (b) R. Faure, J. P. Galy, E. J. Vincent, and J. Elguero, unpublished results; R. Faure, J. P. Galy, E.-J. Vincent, J. P. Fayet, P. Mauret, M. C. Vertut, and J. Elguero, *Can. J. Chem.* **55**, 1728 (1977).

¹⁸⁶ (a) J. D. Bower and F. P. Doyle, *J. Chem. Soc. C*, 727 (1957); (b) G. A. Reynolds and J. A. Van Allan, *J. Org. Chem.* **24**, 1478 (1959); (c) N. P. Bednyagina and I. Ya. Postovskii, *Zh. Obshch. Khim.* **30**, 1431 (1960); (d) E. Alcalde and R. M. Claramunt, *Tetrahedron Lett.*, 1523 (1975).

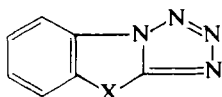
¹⁸⁷ (a) H. Beyer, G. Wolter, and H. Lemke, *Chem. Ber.* **89**, 2550 (1956); (b) E. Alcalde, J. de Mendoza, and J. Elguero, *Chem. Commun.*, 411 (1974); (c) E. Alcalde, J. de Mendoza, and J. Elguero, *J. Heterocycl. Chem.* **11**, 921 (1974).

¹⁸⁸ (a) I. Ya. Postovskii, G. N. Tyurenkova, and L. F. Lipatova, *Dokl. Akad. Nauk SSSR* **179**, 111 (1968); (b) J. V. Singh, *J. Indian Chem. Soc.* **51**, 443 (1974).

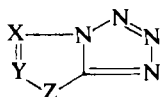
¹⁸⁹ (a) Yu. N. Sheinker, I. Ya. Postovskii, N. P. Bednyagina, L. B. Senyavina, and L. F. Lipatova, *Dokl. Akad. Nauk SSSR* **141**, 1388 (1961); (b) L. F. Avramenko, V. Ya. Pochinok and Yu. S. Rozum, *Zh. Obshch. Khim.* **33**, 980 (1963); (c) R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965).

¹⁹⁰ (a) H. Reimlinger, *Chem. Ber.* **103**, 1900 (1970); (b) R. N. Butler, *Chem. Ind. (London)*, 371 (1973); (c) R. N. Butler, *Adv. Heterocycl. Chem.* **21**, 323 (1977).

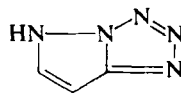
¹⁹¹ E. Lieber and D. R. Levering, *J. Am. Chem. Soc.* **73**, 1313 (1951).



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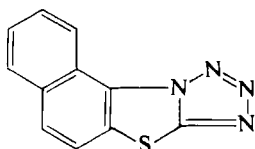
(187)



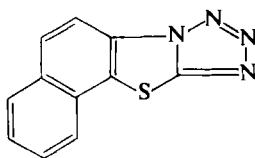
(188)

- a: X = CH₂
 b: X = NR
 c: X = S
 d: X = O

- a: X = Y = CH; Z = S
 b: X = N; Y = CH; Z = NH
 c: X = Y = N; Z = NH
 d: X = Y = CR; Z = NH

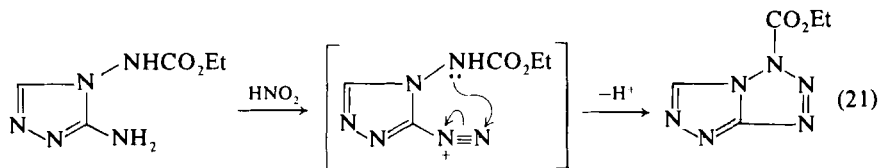


(189)



(190)

Systems containing a tetrazole ring have also been prepared by treatment of heterocyclic diamines with nitrous acid [Eq. (21)].¹⁹²

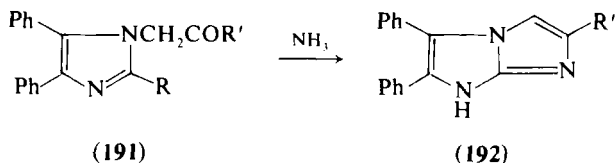


Displacement of halide ion from 2-haloimidazoles (**191**: R = Hal) by ammonia or primary amines has been used as means of introducing a nitrogen atom. In this way, bromoimidazoles (**191**: R = Br) gave imidazo[1,2-*a*]imidazoles (**192**) by cyclization of the intermediate amine (**191**: R = NH₂).^{193a, b, d} Imidazo[1,2-*a*]benzimidazoles were produced in the same way from 1-phenacyl-2-chlorobenzimidazoles,^{193c} and cyclization of 1-(β-haloethyl)-2-haloimidazoles with ammonia gave a 2,3-dihydroimidazo[1,2-*a*]imidazole.¹⁹⁴

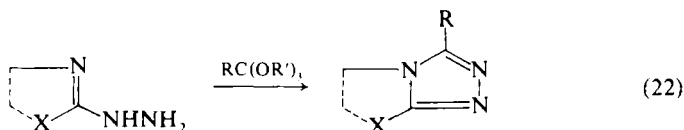
¹⁹² H. Gehlen and K. H. Uteg, *Z. Chem.* **9**, 338 (1969).

¹⁹³ (a) B. A. Priimenko and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **7**, 1243 (1971); (b) M. V. Povstyanoi and P. M. Kochergin, *ibid.* **8**, 816 (1972); (c) V. S. Ponomar and N. G. Kas'yanenko, *Khim. Issled. Farm. USSR*, **52** (1970) [*CA* **76**, 3757 (1972)]; (d) B. A. Priimenko and P. M. Kochergin, *ibid.* **53** (1970) [*CA* **76**, 34170 (1972)].

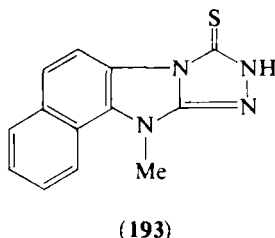
¹⁹⁴ (a) P. M. Kochergin, M. V. Povstyanoi, B. A. Priimenko, and V. S. Ponomar, *Khim. Geterotsikl. Soedin.* **6**, 129 (1970); (b) B. A. Priimenko and P. M. Kochergin, *ibid.* **7**, 1252 (1971).



b. *Introduction of a Carbon Atom.* The *s*-triazole ring in many azapentalenes has been built up by cyclization of orthoesters with hydrazine derivatives [Eq. (22)].



Systems prepared in this way include triazolobenzimidazoles,^{186a, b, 195} triazolobenzothiazoles,^{186a, b, 196, 197} fused *s*-triazolo[3,4-*b*]naphthothiazoles,^{188b} and *s*-triazolo[3,4-*b*]1,3,4-thiadiazoles.¹⁹⁸ The last-named system was also prepared by a modification¹⁹⁸ of Eq. (22) involving the use of carbon disulfide or cyanogen bromide instead of an orthoester. *s*-Triazolo[4,3-*b*]-*s*-triazoles,^{199, 200} 3-mercapto-*s*-triazolo[3,4-*b*]benzothiazole,^{186a} and a fused naphthalene derivative **193**²⁰¹ were prepared using carbon disulfide or cyanogen bromide.



Cyclization of *N*-aminoazoles with orthoesters, acids, acid chlorides, etc., constitutes another general route to fused *s*-triazoles or 1,3,4-

¹⁹⁵ J. de Mendoza and J. Elguero, *Bull. Soc. Chim. Fr.*, 1675 (1974).

¹⁹⁶ (a) E. B. Knott and L. A. Williams, U.S. Patent 2,861,076 (1958) [*CA* **53**, 9251 (1959)]; (b) J. A. Van Allan, U.S. Patent 2,891,862 (1959) [*CA* **54**, 4224 (1960)].

¹⁹⁷ (a) T. P. Sycheva, I. D. Kiseleva, G. P. Syrova, and M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **6**, 913 (1970); (b) **6**, 916 (1970).

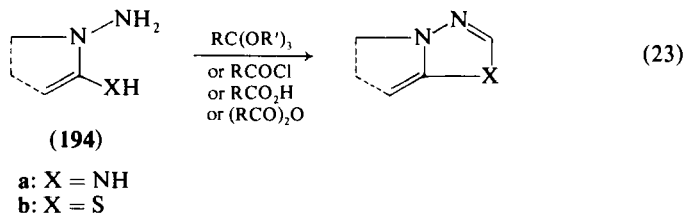
¹⁹⁸ (a) M. Kanaoka, *Chem. Pharm. Bull.* **5**, 385 (1957); (b) K. T. Potts and R. M. Huseby, *J. Org. Chem.* **31**, 3528 (1966).

¹⁹⁹ K. T. Potts and C. A. Hirsch, *Chem. Ind. (London)*, 2168 (1966).

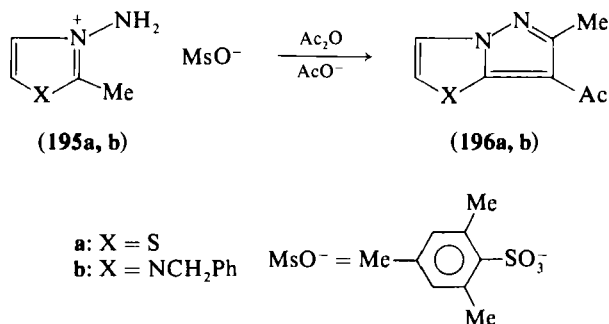
²⁰⁰ K. T. Potts and C. A. Hirsch, *J. Org. Chem.* **33**, 143 (1968).

²⁰¹ I. N. Getsova, L. L. Sribnaya and N. P. Bednyagina, *Khim. Geterotsikl. Soedin.* **1**, 129 (1965).

thiadiazoles [Eq. (23)]. From the appropriate diamino derivative **194a**, *s*-triazolo[4,3-*b*]-*s*-triazoles,^{137, 202a-d} thiazolo[3,2-*b*]-*s*-triazoles,^{202e} *s*-triazolo[1,5-*a*]benzimidazoles,²⁰³ and imidazo[1,2-*b*]-*s*-triazoles²⁰⁴ have been obtained. *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazoles have been prepared from the corresponding 4-amino-5-mercapto-*s*-triazole (**194b**) in the presence of formic acid.^{126, 146a} Two recently reported mesoionic triazolothiadiazoles were prepared in a similar way.^{146b}



1-Amino-2-methylthiazolium salts (**195a**) and 1-amino-3-benzyl-2-methylimidazolium salts (**195b**) react readily with acetic anhydride and sodium acetate to give the pyrazolo[5,1-*b*]thiazole (**196a**) and the imidazo[1,2-*b*]pyrazole (**196b**), respectively. This reaction presumably involves acetylation of the activated methyl group followed by ring closure. *N*-Amino-2-methylbenzothiazolium salts give a related pyrazolo[5,1-*b*]benzothiazole.²⁰⁵



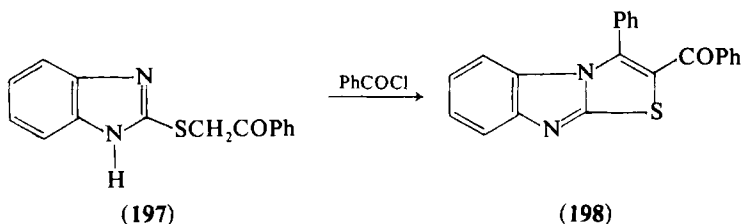
²⁰² (a) H. Gehlen and G. Röbisch, *Justus Liebigs Ann. Chem.* **660**, 148 (1962); (b) F. Kurzer and L. E. A. Godfrey, *Angew. Chem., Int. Ed. Engl.* **2**, 459 (1963); (c) R. G. Child and A. S. Tomcufcik, *J. Heterocycl. Chem.* **2**, 302 (1965); (d) F. Kurzer, *J. Chem. Soc. C*, 1813 (1970); (e) H. Hoffman and I. Hammann (Bayer A.-G.), U.S. Patent 3,682,943 (1972) [*CA* **77**, 140084 (1972)].

²⁰³ R. I-Fu Ho and A. R. Day, *J. Org. Chem.* **38**, 3084 (1973).

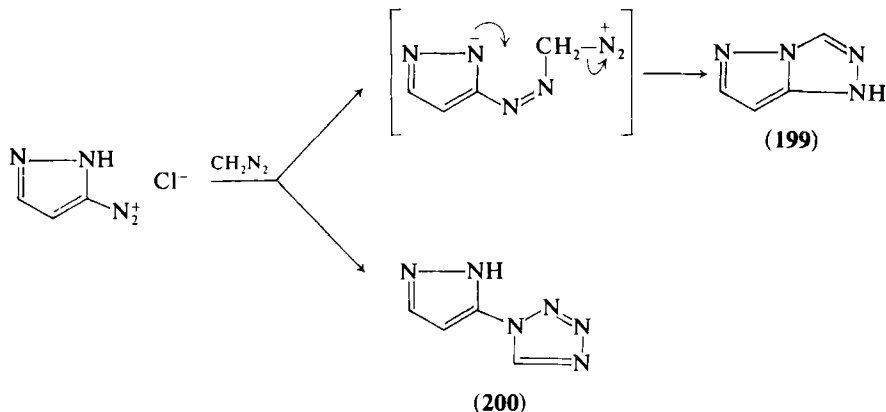
²⁰⁴ (a) A. Hetzheim and G. Manthey, *Chem. Ber.* **103**, 2845 (1970); (b) A. Hetzheim, H. Pusch, and H. Beyer, *ibid.* **103**, 3533 (1970); (c) A. Hetzheim and H. Pusch, *Z. Chem.* **10**, 385 (1970).

²⁰⁵ H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 482 (1974).

Akasaki and Ohno²⁰⁶ recently found that *S*-phenacyl-2-mercapto-benzimidazole (**197**) on treatment with benzoyl chloride did not give the expected *N*-benzoyl derivative but the benzimidazothiazole **198** in quantitative yield. Exploration of the mechanism revealed a complicated sequence of acyl migrations, which, though not yet fully elucidated, may have important biochemical implications, particularly on the mode of action of biotin.



Pyrazolo[3,2-*c*]-s-triazole (**199**) was isolated in low yield (1%), along with the tetrazolylpyrazole (**200**), when 3(5)-pyrazole diazonium chloride was treated with one equivalent of diazomethane.²⁰⁷

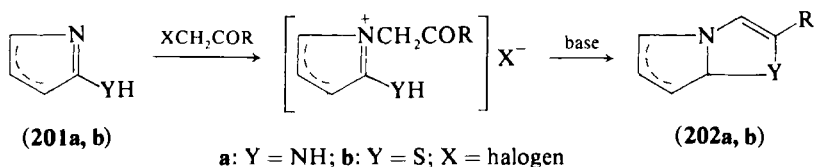


3. [3 + 2] Syntheses

a. *The Tschitschibabin Reaction.* Perhaps the most useful and widely employed synthesis of fused imidazoles (**202a**) and fused thiazoles (**202b**) is the Tschitschibabin method involving the reaction of heterocyclic amines **201a** or thiols **201b** with α -halogenocarbonyl compounds (Scheme 7).

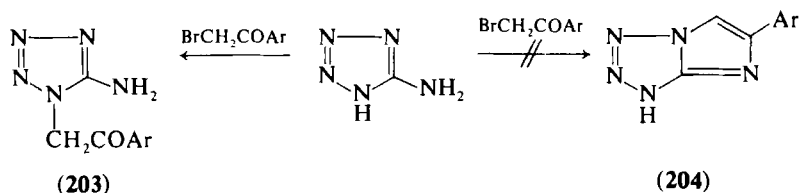
²⁰⁶ Y. Akasaki and A. Ohno, *J. Am. Chem. Soc.* **96**, 1957 (1974).

²⁰⁷ H. Reimlinger and R. Merényi, *Chem. Ber.* **103**, 3284 (1970).



SCHEME 7

Some systems have been obtained by a modification of the above procedure in which propargyl bromide replaces the α -halogenoketone. Table II summarizes the systems that have been prepared by the Tschitschibabin reaction, together with the preparative route used. However, certain difficulties are encountered with this method. The syntheses of imidazo[1,2-*b*]-s-triazoles and imidazo[1,2-*d*]tetrazoles have been reported,^{208b} but repetition of this work more recently²⁰⁹ has cast doubt on these results. 5-Aminotetrazole was found to react with arylacyl bromides to give products shown to be *N*-substituted tetrazoles **203** and not imidazo[1,2-*d*]tetrazoles (**204**) as previously suggested.^{208b}



The failure of the Tschitschibabin reaction has also been observed with other NH-aminoazoles. Werbel and Zamora²¹⁴ found that 2-amino-1-methylbenzimidazole reacted rapidly with phenacyl bromide to give an intermediate that cyclized easily to the imidazo[1,2-*a*]benzimidazole, but 2-aminobenzimidazole gave no product. In the same way, 2-aminothiazole yielded a bicyclic system but 3-amino-*s*-triazole did not.²²⁵

²⁰⁸ (a) L. Almirante, A. Mugnaini, L. Polo Friz, and E. Provinciali, *Boll. Chim. Farm.* **105**, 32 (1966); (b) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi, and W. Murmann, *J. Med. Chem.* **9**, 29 (1966).

²⁰⁹ R. M. Claramunt, R. Granados, and E. Pedrosa, *Bull. Soc. Chim. Fr.*, 1854 (1973).

²¹⁰ (a) P. M. Kochergin and B. A. Priimenko, *Khim. Geterotsikl. Soedin.* **5**, 176 (1969); (b) **7**, 1692 (1971).

²¹¹ H. Beyer, *Z. Chem.* **10**, 289 (1970).

²¹² L. F. Miller and R. E. Bambury, *J. Med. Chem.* **15**, 415 (1972).

²¹³ A. M. Simonov and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **1**, 316 (1965).

²¹⁴ L. M. Werbel and M. L. Zamora, *J. Heterocycl. Chem.* **2**, 287 (1965).

²¹⁵ (a) P. M. Kochergin and A. M. Simonov, *Khim. Geterotsikl. Soedin., Sb. 1*, 133 (1967) [*CA* **70**, 96712 (1969)]; (b) 137 (1967) [*CA* **70**, 96705 (1969)].

²¹⁶ A. M. Simonov and V. A. Anisimova, *Khim. Geterotsikl. Soedin.* **4**, 1102 (1968).

Generally speaking, 2-aminothiazoles, -oxazoles, and N-substituted imidazoles react with α -halogenoketones more easily than NH compounds, though 2-amino-4,5-dimethyloxazole and 3-amino-1-methyl-4-phenylpyrazole are reported²¹⁴ not to undergo the Tschitschibabin reaction.

2-Amino-1,3,4-oxadiazoles (**205**) on treatment with α -halogenoketones gave intermediate quaternary salts **206** that did not cyclize directly to imidazo[2,1-*b*]oxadiazoles (**208**) with base. Hydrolysis of **206** with aqueous potassium carbonate caused ring-opening at C-2 with subsequent closure to the imidazolone **207**. These latter compounds could be cyclized to **208** with phosphorus oxychloride.^{204c, 211, 246}

TABLE II
SYSTEMS PREPARED BY THE TSCHITSCHIBABIN REACTION

System	Method ^a	References
Imidazo[1,2- <i>a</i>]imidazole	Aa	193d, 210–212, 204c
Imidazo[1,2- <i>a</i>]benzimidazole	Aa	213–220
Imidazo[2,1- <i>b</i>]thiazole	Aa	208, 221–233
	Ab	224b
	Ba	247a, b, 248–254
Imidazo[5,1- <i>b</i>]thiazole	Ba	247c, 247d
Imidazo[2,1- <i>b</i>]benzothiazole	Aa	152, 224b, 225, 234–238
	Ab	224b, 236
	Aa	239
Imidazo[2,1- <i>b</i>]-1,3,4-thiadiazole	Aa	214, 240–242
	Ab	242
Imidazo[2,1- <i>b</i>]-1,3,4-selenadiazole	Aa	243
Imidazo[1,2- <i>b</i>]- <i>s</i> -triazole	Aa	244, 268b
Imidazo[2,1- <i>c</i>]- <i>s</i> -triazole	Aa	268
Imidazo[2,1- <i>b</i>]benzoxazole	Aa	152b, 214
Imidazo[1,2- <i>b</i>]pyrazole	Aa	245
Thiazolo[3,2- <i>a</i>]benzimidazole	Ab	236
	Ba	130b, 255–262
Naphtho[1,2- <i>d</i>]imidazo[3,2- <i>b</i>]thiazole	Ba	263
Thiazolo[2,3- <i>c</i>]- <i>s</i> -triazole	Ba	249, 264–266
Thiazolo[3,2- <i>b</i>]- <i>s</i> -triazole	Ba	249, 264–267
Thiazolo[3,2- <i>d</i>]tetrazolium salts	Ba	41

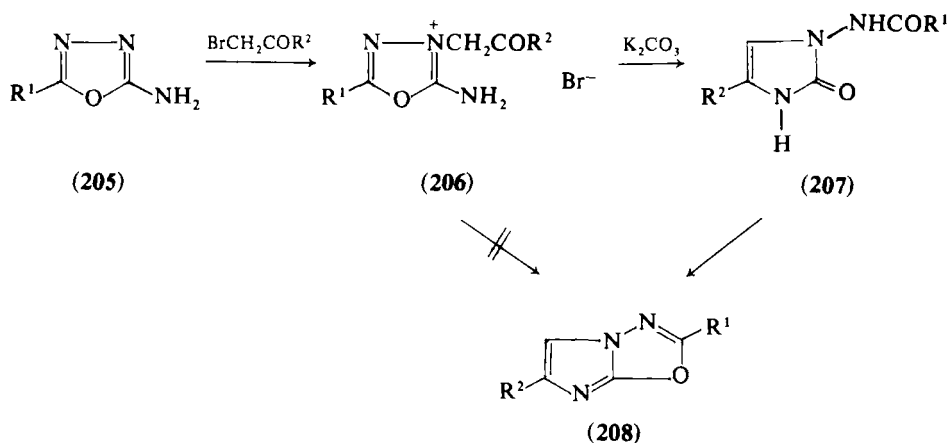
^a A: Tschitschibabin reaction in Scheme 7 with Y = NH; B: Tschitschibabin reaction in Scheme 7 with Y = S; a: α -halogeno ketone used; b: propargyl bromide used.

²¹⁷ A. M. Simonov, V. A. Anisimova, and L. E. Grushina, *Khim. Geterotsikl. Soedin.* **6**, 838 (1970).

²¹⁸ H. Ogura, H. Takayanagi, Y. Yamazaki, S. Yonezawa, H. Takagi, S. Kobayashi, T. Kamioka, and K. Kamoshita, *J. Med. Chem.* **15**, 923 (1972).

²¹⁹ A. M. Simonov, V. A. Anisimova, and T. A. Borisova, *Khim. Geterotsikl. Soedin.* **9**, 111 (1973).

- ²²⁰ B. I. Khristich, G. M. Suvorova, and A. M. Simonov, *Khim. Geterotsikl. Soedin.* **10**, 1398 (1974).
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- ²²² B. Kickhöfen and F. Kröhnke, *Chem. Ber.* **88**, 1109 (1955).
- ²²³ (a) T. Pyl, R. Giebelmann, and H. Beyer, *Justus Liebigs Ann. Chem.* **643**, 145 (1961); (b) T. Pyl, L. Bülling, K. H. Wünsch, and H. Beyer, *ibid.* **643**, 153 (1961); (c) T. Pyl, K. H. Wünsch, L. Bülling, and H. Beyer, *ibid.* **657**, 113 (1962).
- ²²⁴ (a) M. Mazière, N.-P. Buu-Hoi, and N. Dat Xuong, *Bull. Soc. Chim. Fr.*, 1000 (1963); (b) I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* **12**, 813 (1964).
- ²²⁵ N.-P. Buu-Hoi, N. Dat Xuong, and Ta Thu-Cuc, *Bull. Soc. Chim. Fr.*, 1277 (1966).
- ²²⁶ L. Pentimalli, G. Cogo, and A. M. Guerra, *Gazz. Chim. Ital.* **97**, 488 (1967).
- ²²⁷ N. O. Saldabol, G. Ya. Zarinya, and S. A. Hiller, *Khim. Geterotsikl. Soedin.* **4**, 178 (1968).
- ²²⁸ D. W. Dunwell and D. Evans, *J. Chem. Soc. C*, 1615 (1971).
- ²²⁹ G. Kempter, J. Spindler, H. J. Fiebig, and G. Sarodnick, *J. Prakt. Chem.* **313**, 977 (1971).
- ²³⁰ L. Marchetti, L. Pentimalli, P. Lazzeretti, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1926 (1973).
- ²³¹ J. F. Robert, A. Xicluna, and J. J. Panouse, *Eur. J. Med. Chem.* **10**, 59 (1975).
- ²³² B. S. Drach, I. Yu. Dolgushina, and A. D. Sinitsa, *Khim. Geterotsikl. Soedin.* **10**, 928 (1974).
- ²³³ P. M. Kochergin, A. N. Krasovskii, N. P. Grin, and E. I. Bogatyreva, USSR Patent 436,058 (1974) [CA **82**, 31326 (1975)].
- ²³⁴ J. Parrick and K. Pearson, *Chem. Ind. (London)*, 1261 (1970).
- ²³⁵ N. P. Grain, *Khim. Issled. Farm. USSR*, 17 (1970) [CA **76**, 25172 (1972)].
- ²³⁶ S. Kano, *Yakugaku Zasshi* **92**, 927 (1972) [CA **77**, 114304 (1972)].
- ²³⁷ N. P. Grin, A. N. Krasovskii, and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **8**, 1271 (1972).
- ²³⁸ P. M. Kochergin, A. N. Krasovskii, and N. P. Grin, USSR Patent 443,039 (1974) [CA **82**, 31325 (1975)].
- ²³⁹ J. V. Singh, *J. Indian Chem. Soc.* **51**, 559 (1974).
- ²⁴⁰ T. Matsukawa and S. Ban, *J. Pharm. Soc. Jpn.* **72**, 610 (1952).
- ²⁴¹ T. Pyl, F. Waschk, and H. Beyer, *Justus Liebigs Ann. Chem.* **663**, 113 (1963).
- ²⁴² S. Kano, *Yakugaku Zasshi* **92**, 935 (1972) [CA **77**, 126492 (1972)].
- ²⁴³ I. Lalezari and A. Shafiee, *J. Heterocycl. Chem.* **8**, 835 (1971).
- ²⁴⁴ A. Kreutzberger and B. Meyer, *Chem. Ber.* **105**, 1810 (1972).
- ²⁴⁵ J. Elguero, R. Jacquier, and S. Mignonac-Mondon, *J. Heterocycl. Chem.* **10**, 411 (1973).
- ²⁴⁶ (a) H. Beyer and A. Hetzheim, *Z. Chem.* **2**, 152 (1962); (b) *Chem. Ber.* **97**, 1031 (1964); (c) G. Westphal and P. Henklein, *Z. Chem.* **9**, 25 (1969).
- ²⁴⁷ (a) E. Ochiai, *Chem. Ber.* **69**, 1650 (1936); (b) P. M. Kochergin and M. N. Shchukina, *Zh. Obshch. Khim.* **26**, 458 (1956); (c) P. M. Kochergin and A. M. Tsyganova, *Khim. Geterotsikl. Soedin.* **1**, 313 (1965); (d) **3**, 93 (1967).
- ²⁴⁸ (a) I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **6**, 508 (1970); (b) **6**, 512 ((1970); (c) I. A. Mazur, P. M. Kochergin, and G. S. Tkachenko, *ibid.* **6**, 824 (1970); (d) I. A. Mazur, P. M. Kochergin, and V. G. Tromsa, *ibid.* **7**, 389 (1971).
- ²⁴⁹ R. S. Shadbolt, *J. Chem. Soc. C*, 1667 (1971).
- ²⁵⁰ V. P. Arya and S. P. Ghate, *Indian J. Chem.* **9**, 1204 (1971).
- ²⁵¹ A. Mustafa, M. I. Ali, M. A. Abou-State, and A. E. G. Hammam, *J. Prakt. Chem.* **314**, 785 (1972).



b. *Ring-Closure of Enol-betaine Intermediates.* While studying the action of sodium bicarbonate on 1-phenacyl-2-methylpyridinium bromide, Tschitschibabin²⁶⁹ effected ring closure and thus the first

²⁵² J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.* **11**, 747 (1973).

²⁵³ (a) V. K. Chadha, H. S. Chaudhary, and H. K. Pujari, *Indian J. Chem.* **8**, 885 (1970); (b) K. S. Dhaka, V. K. Chadha, and K. Pujari, *Aust. J. Chem.* **26**, 435 (1973); (c) J. F. Robert and J. J. Panouse, *C.R. Hebd. Seances Acad. Sci., Ser. C.* **278**, 1289 (1974).

²⁵⁴ G. de Stevens and A. Halamandaris, *J. Am. Chem. Soc.* **79**, 5710 (1957).

²⁵⁵ A. N. Krasovskii and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **3**, 899 (1967).

²⁵⁶ H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.* **16**, 2167 (1968).

²⁵⁷ I. I. Chizhevskaya, N. N. Khovratovich, and Z. M. Grabovskaya, *Khim. Geterotsikl. Soedin.* **4**, 443 (1968).

²⁵⁸ A. N. Krasovskii and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **5**, 321 (1969).

²⁵⁹ H. Ogura, T. Itoh, and K. Kikuchi, *J. Heterocycl. Chem.* **6**, 797 (1969).

²⁶⁰ A. N. Krasovskii, P. M. Kochergin, and L. V. Samoilenko, *Khim. Geterotsikl. Soedin.* **6**, 827 (1970).

²⁶¹ A. N. Krasovskii, P. M. Kochergin, and T. E. Kozlovskaya, *Khim. Geterotsikl. Soedin.* **7**, 393 (1971).

²⁶² (a) J. Mohan and H. K. Pujari, *Indian J. Chem.* **10**, 274 (1972); (b) J. Mohan, V. K. Chadha, and H. K. Pujari, *ibid.* **11**, 1119 (1973).

²⁶³ E. G. Knysh, A. N. Krasovskii, P. M. Kochergin, and P. M. Shabel'nik, *Khim. Geterotsikl. Soedin.* **8**, 399 (1972).

²⁶⁴ K. T. Potts, *Chem. Rev.* **61**, 87 (1961).

²⁶⁵ K. T. Potts and S. Husain, *J. Org. Chem.* **36**, 10 (1971).

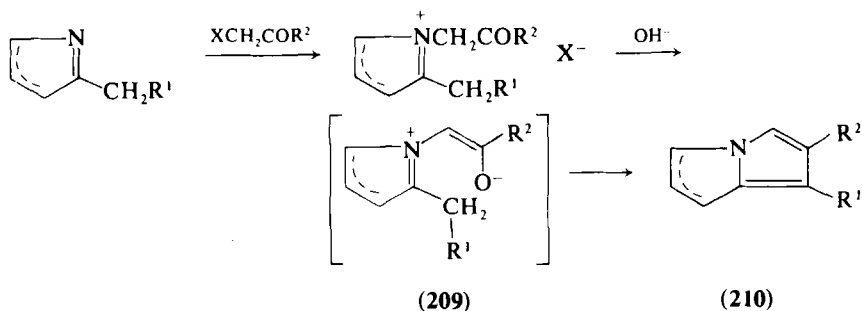
²⁶⁶ M. M. Kochhar and B. B. Williams, *J. Med. Chem.* **15**, 332 (1972).

²⁶⁷ K. S. Dhaka, J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.* **12**, 485 (1974).

²⁶⁸ (a) L. Alyusufi, V. N. Bubnovskaya, and F. S. Babichev, *Ukr. Khim. Zh.* **39**, 1289 (1973); (b) R. Faure, E. J. Vincent, R. M. Claramunt, J. M. Fabregà, and J. Elguero, *Tetrahedron* **32**, 341 (1976).

²⁶⁹ (a) A. E. Tschitschibabin, *Chem. Ber.* **60**, 1607 (1927); (b) **62**, 1068 (1929).

synthesis of pyrrolo[1,2-*a*]pyridine (indolizine) derivatives. A modification of this synthesis has been used to prepare azapentalenes with a fused pyrrole ring **210** (Scheme 8). The structure of the intermediate enolbetaine **209** has been confirmed by physicochemical studies.



SCHEME 8

Pyrrolo[2,1-*b*]thiazoles,^{28, 29, 270–273} pyrrolo[1,2-*a*]imidazoles,^{38, 274–277} pyrrolo[1,2-*a*]benzimidazoles,^{38, 278–288} pyrrolo[1,2-*b*]-*s*-triazoles,²⁸⁹ and pyrrolo[2,1-*c*]-*s*-triazoles²⁹⁰ have been prepared by this route.

²⁷⁰ H. Kondo and F. Nagasawa, *J. Pharm. Soc. Jpn.* **57**, 308 (1937).

²⁷¹ (a) T. Pyl, H. Gille, and D. Nusch, *Justus Liebigs Ann. Chem.* **679**, 139 (1964); (b) T. Pyl, H. D. Dinse, and O. Sietz, *ibid.* **676**, 141 (1964).

²⁷² (a) H. Erlenmeyer, O. Weber, P. Schmidt, G. Küng, C. Zinsstag, and B. Prijs, *Helv. Chim. Acta* **31**, 1142 (1948); (b) W. Traupel, M. Erne, and E. Sorkin, *ibid.* **33**, 1960 (1950).

²⁷³ T. Pyl and K. H. Wünsch, *Z. Chem.* **5**, 361 (1965).

²⁷⁴ A. A. Druzhinina and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **3**, 527 (1967); (b) **3**, 532 (1967).

²⁷⁵ A. A. Druzhinina, P. M. Kochergin, and N. P. Bychkova, *Khim. Geterotsikl. Soedin.* **5**, 856 (1969).

²⁷⁶ A. A. Druzhinina, P. M. Kochergin, and L. M. Alekseeva, *Khim. Geterotsikl. Soedin.* **8**, 405 (1972).

²⁷⁷ A. A. Druzhinina and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **3**, 532 (1967).

²⁷⁸ F. S. Babichev and A. F. Babicheva, *Khim. Geterotsikl. Soedin.* **3**, 187 (1967).

²⁷⁹ R. M. Palei and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **3**, 536 (1967).

²⁸⁰ F. S. Babichev and A. F. Babicheva, *Khim. Geterotsikl. Soedin.* **3**, 917 (1967).

²⁸¹ M. Yu. Kornilov, G. G. Dyadyusha, and F. S. Babichev, *Khim. Geterotsikl. Soedin.* **4**, 905 (1968).

²⁸² R. M. Palei and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **5**, 865 (1969).

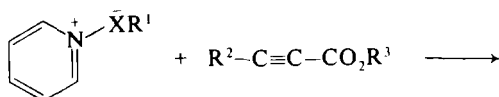
²⁸³ R. M. Palei and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **5**, 1075 (1969).

²⁸⁴ R. M. Palei and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **6**, 572 (1970).

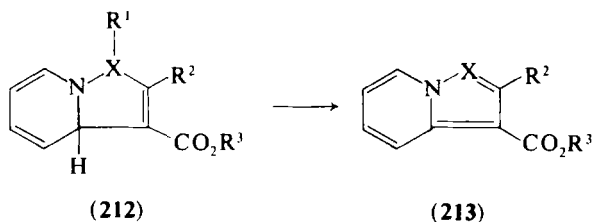
²⁸⁵ (a) F. S. Babichev, T. Nguyen, P. Nguyen, and M. Yu. Kornilov, *Ukr. Khim. Zh.* **36**, 819 (1970) [*CA* **74**, 76366 (1971)]; (b) F. S. Babichev, G. P. Kutrov, and M. Yu. Kornilov, *ibid.* **36**, 909 (1970) [*CA* **74**, 76367 (1971)].

²⁸⁶ P. Nguyen, Zh. M. Ivanova, G. I. Derkack, and F. S. Babichev, *Zh. Obshch. Khim.* **4**, 319 (1971).

c. *1,3-Dipolar Cycloadditions.* Despite the proved usefulness of 1,3-dipolar cycloaddition reactions for synthesizing five-membered ring heterocycles,²⁹¹ few azapentalenes of type B have been prepared by this route (cf. Section III,A,3,d). However, cycloaddition reactions have been used to prepare a number of indolizine and azaindolizine systems by a general method illustrated in Scheme 9. A pyridinium *N*-imine or *N*-ylid (**211**), usually generated by deprotonation of the corresponding quaternary salt, reacts with a dipolarophile to give an adduct **212**, which aromatizes, often during the reaction, to produce an indolizine derivative^{291, 292} (**213**).



- (211) a: $\text{X} = \text{C}(\text{CN})$; $\text{R}^1 = \text{CN}$
 b: $\text{X} = \text{CCOPh}$; $\text{R}^1 = \text{H}$
 c: $\text{X} = \text{N}$; $\text{R}^1 = \text{H}$



SCHEME 9

Boekelheide and Fedoruk³² applied this reaction with success to the synthesis of a pyrrolo[1,2-*a*]imidazole (**214**) [Eq. (24)] using the same conditions that had been used for the corresponding pyridinium ylid. Excess of ethyl propiolate was thought to act as the dehydrogenating agent. Pyrrolo[1,2-*a*]benzimidazoles (e.g., **215**) were prepared in the

²⁸⁷ V. A. Kovtunenکو and F. S. Babichev, *Ukr. Khim. Zh.* **38**, 1244 (1972) [*CA* **78**, 72007 (1973)].

²⁸⁸ R. M. Palei and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **8**, 403 (1972).

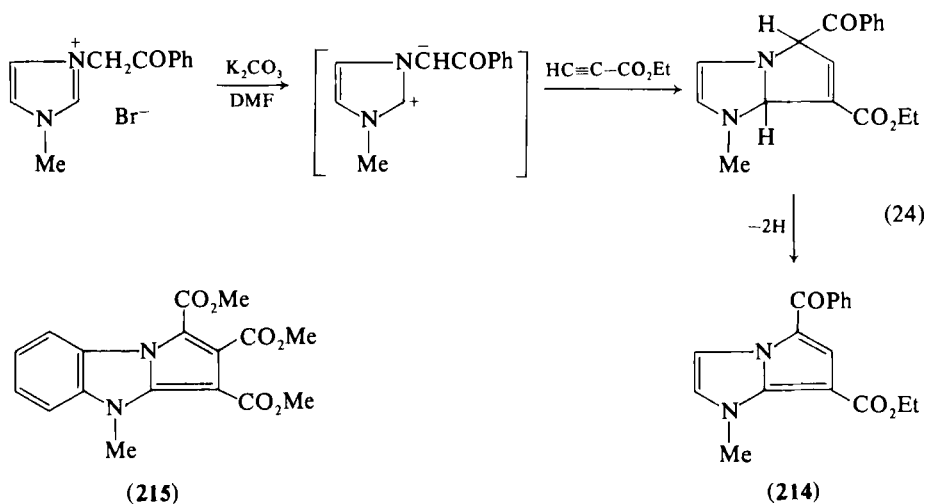
²⁸⁹ (a) V. A. Kovtunenکو and F. S. Babichev, *Ukr. Khim. Zh.* **38**, 1142 (1972) [*CA* **78**, 58327 (1973)]; (b) H. G. O. Becker, H. D. Steinleitner, and H. J. Timpe, *Synthesis*, 414 (1973); (c) F. S. Babichev and V. A. Kovtunenکو, *Ukr. Khim. Zh.* **41**, 181 (1975) [*CA* **83**, 164082 (1975)].

²⁹⁰ F. S. Babichev, V. A. Kovtunenکو, and L. N. Didenکو, *Ukr. Khim. Zh.* **40**, 245 (1974) [*CA* **80**, 133356 (1974)].

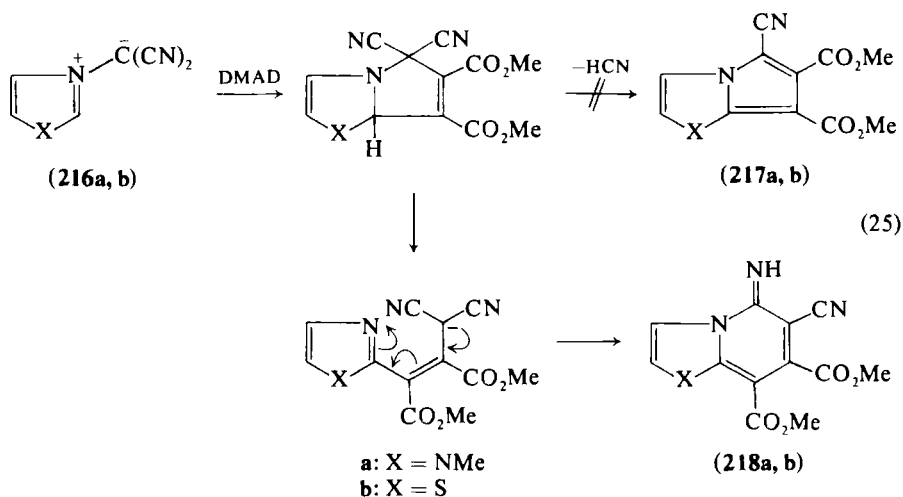
²⁹¹ R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **2**, 565 (1963); *Bull. Soc. Chim. Fr.*, 3431 (1965); *Helv. Chim. Acta* **50**, 2421 (1967) and references therein.

²⁹² H. J. Timpe, *Adv. Heterocycl. Chem.* **17**, 213 (1974).

same way, by addition to dimethyl acetylenedicarboxylate (DMAD).²⁹³⁻²⁹⁵



However, the dicyano ylids (216a, b) failed to give the aromatic azapentalenes 217 with DMAD. The products isolated were the iminoazapyrrocoline 218a or the fused thiazole 218b as shown in Eq. (25).



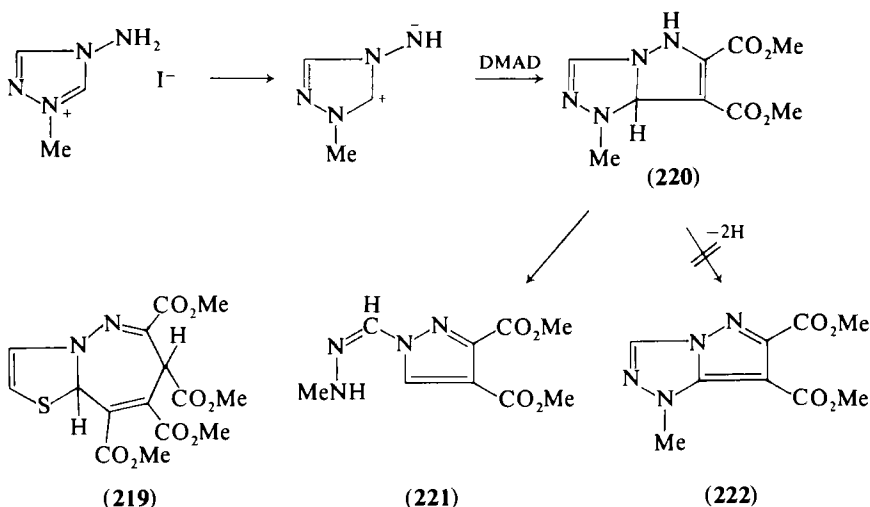
²⁹³ H. Ogura, M. Kawano, K. Kikuchi, and T. Itoh, *Int. Congr. Heterocycl. Chem.*, 3rd, 506 (1971). Commun. D-26-9.

²⁹⁴ H. Ogura and K. Kikuchi, *J. Org. Chem.* **37**, 2679 (1972).

²⁹⁵ (a) I. Zugrăvescu, J. Herdan, and I. Drută, *Rev. Roum. Chim.* **19**, 649 (1974); (b) **19**, 659 (1974).

Loss of HCN from the intermediate adduct failed to occur, though the related pyridinium ylid **211a** underwent addition with loss of HCN to give an aromatic system (**213**: $X = C(CN)_2$).²⁹⁶ A compound analogous to **218** was also isolated during the preparation of **215**.^{294, 295a}

Certain *N*-imines formed by deprotonation of *N*-aminoazolum salts also failed to undergo cycloaddition to give azapentalenes. *N*-Amino-thiazolium mesylate on treatment with potassium carbonate and DMAD added 2 moles of dipolarophile to give the fused diazepine **219**.²⁰⁵ 4-Amino-1-methyl-*s*-triazolium iodide and DMAD in the presence of base gave the pyrazole **221**, probably by ring opening of the first-formed adduct **220**. Dehydrogenation to **222** did not occur.²⁹⁷



In the same way, *N*-imines generated from 1-aminobenzimidazolium salts underwent cycloaddition with DMAD to give an adduct that opened in the presence of base in an identical manner [Eq. (26)].²⁹⁸ Loss of hydrogen when R^2 was H was not observed.

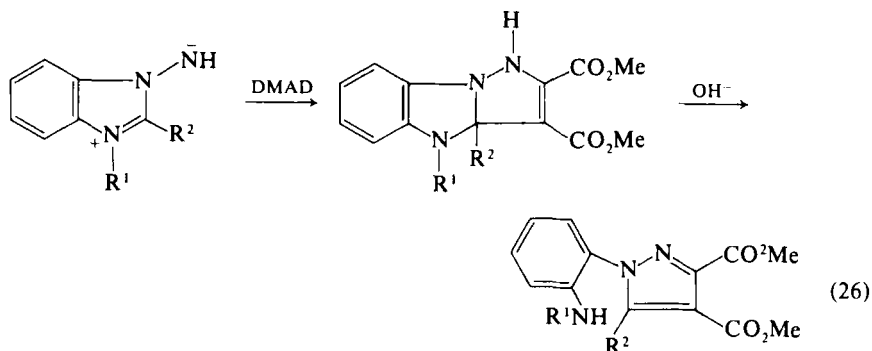
The pyrrolo[1,2-*c*]imidazole (**223**) was produced by addition of DMAD to an azomethine ylid resulting from photochemical ring opening of a fused aziridine,²⁹⁹ and the adduct **224** resulted from

²⁹⁶ W. J. Linn, O. W. Webster, and R. E. Benson, *J. Am. Chem. Soc.* **87**, 3651 (1965).

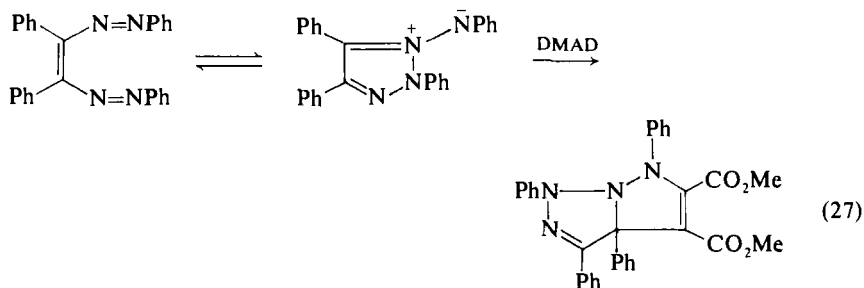
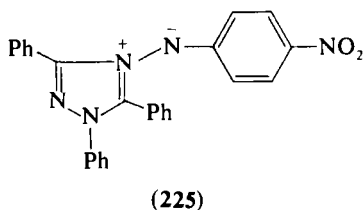
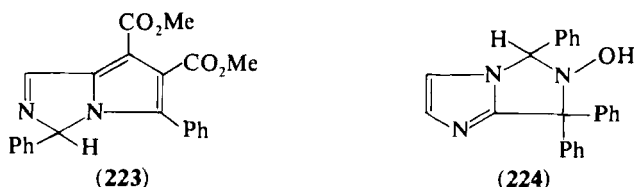
²⁹⁷ A. J. H. Summers and J. Elguero, *Bull. Soc. Chim. Fr.*, 3974 (1972). The structure of the product originally proposed in this paper has since been shown to be incorrect (J. Elguero, unpublished results).

²⁹⁸ Y. Tamura, H. Hayashi, Y. Nishimura, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 225, 819 (1975).

²⁹⁹ (a) H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.* **33**, 1097 (1968); (b) A. Padwa and E. Glazer, *J. Org. Chem.* **38**, 284 (1973).



addition of *anti*-benzaldoxime to 6,6-diphenyl-1,4-diazafluvene.³⁰⁰ A *v*-triazolium *N*-imine (which was thought to exist in equilibrium with the bisazoethylene) gave an adduct with DMAD [Eq. (27)],³⁰¹ but the same reaction with **225** failed to yield an isolable product.³⁰²

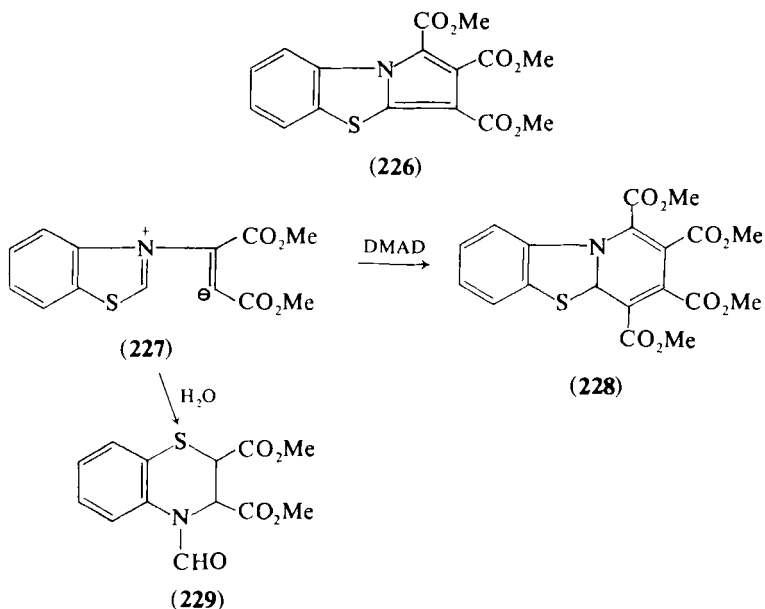


³⁰⁰ W. Rohr, R. Swoboda, and H. Staab, *Chem. Ber.* **101**, 3491 (1968).

³⁰¹ C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971).

³⁰² A. J. H. Summers, Ph.D. Thesis, London (1970).

Finally, recent work has disproved the originally proposed structure **226**³⁰³ of the product from addition of DMAD to benzothiazole. McKillop and Sayer³⁰⁴ have shown that a first-formed adduct **227** can give a fused thiazole **228** by addition of a second DMAD molecule, or rearrange to the benzothiazine **229** in the presence of water. The structure of **229** was established by X-ray crystallography.³⁰⁵



d. *Formation of Fused Tetrazoles with Sodium Azide.* Sodium azide displaces halide ion from halogenoazoles, or nitrogen from azole diazonium salts, to give fused tetrazoles [Eq. (28)] (see also Section III,B,2,a). 6-Aryl-1,3,4-thiadiazolo[3,2-*d*]tetrazoles have been prepared in this way from the corresponding 2-chloro-1,3,4-thiadiazole,³⁰⁶ and thiazolo[3,2-*d*]tetrazoles,³⁰⁷ imidazo[1,2-*d*]tetrazoles,^{186d} and *s*-triazolo-

³⁰³ D. H. Reid, F. S. Skelton, and W. Bonthron, *Tetrahedron Lett.*, 1797 (1964).

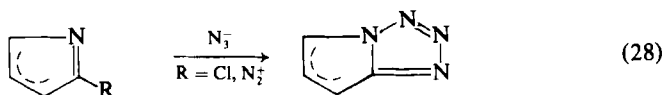
³⁰⁴ A. McKillop and T. S. B. Sayer, *Tetrahedron Lett.*, 3081 (1975); A. McKillop, T. S. B. Sayer, and G. C. A. Bellinger, *J. Org. Chem.*, **41**, 1328 (1976).

³⁰⁵ H. Ogura, H. Takayanagi, K. Furuhashi, and Y. Iitaka, *Chem. Commun.*, 759 (1974); H. Ogura, K. Kikuchi, H. Takayanagi, K. Furuhashi, Y. Iitaka, and R. M. Acheson, *J. Chem. Soc. Perkin Trans 1*, 2316 (1975); P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *ibid.* 1269 (1976).

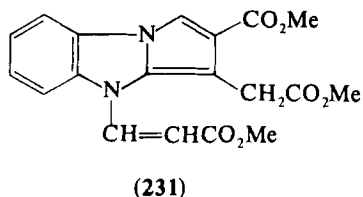
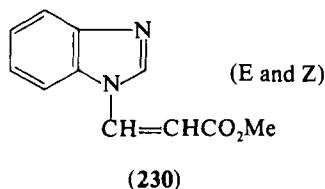
³⁰⁶ (a) T. Bacchetti, A. Alemagna, and B. Danieli, *Ann. Chim. (Rome)* **55**, 615 (1965); (b) A. Alemagna, T. Bacchetti, and P. Beltrame, *Tetrahedron* **24**, 3209 (1968).

³⁰⁷ (a) L. F. Avramenko, T. A. Zakharova, V. Ya. Pochinok, and Yu. S. Rozum, *Khim. Geterotsikl. Soedin.* **4**, 423 (1968); (b) R. Faure, J. P. Galy, E. J. Vincent, and J. Elguero, *Bull. Soc. Chim. Belg.* **84**, 1189 (1975).

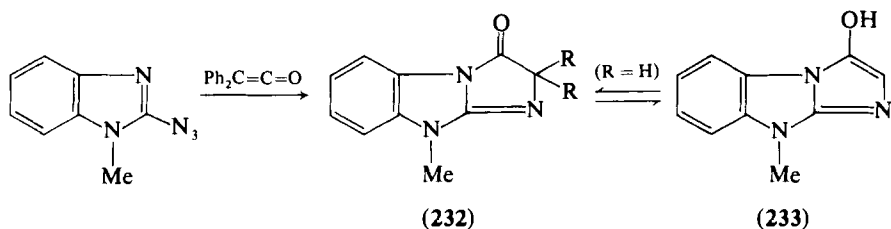
[2,3-*d*]tetrazoles,^{308, 309} have been obtained from the appropriate diazonium salts. Tetrazole \rightleftharpoons azide isomerism is discussed later (Section IV,B,1).



e. *Miscellaneous Syntheses.* As part of a study of the reactions of ethyl propiolate with heterocycles, Acheson and Verlander³¹⁰ found that reaction with benzimidazole in the absence of solvent gave the pyrrolo-benzimidazole **231** and the N-substituted benzimidazole **230**.



2-Azido-1-methylbenzimidazole with diphenylketene gave the imidazobenzimidazole (**232**: R = Ph), but decomposition of the azide to give a nitrene, followed by cycloaddition to the ketene, was ruled out as a mechanism. Instead, the authors propose that **232** is formed by attack of the endocyclic ring nitrogen on the C=C bond of the ketene followed by nucleophilic displacement of N₂ from the azide.¹⁶⁸ Preparation of an analog (**232**, R = H) would constitute a possible route to an aromatic azapentalene **233**.

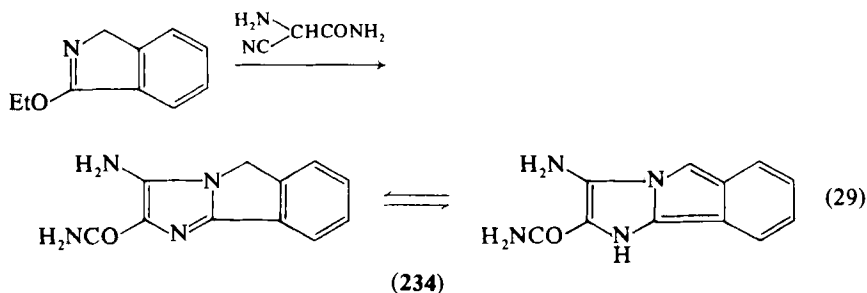


³⁰⁸ B. T. Heitke and C. G. McCarty, *J. Org. Chem.* **39**, 1522 (1974).

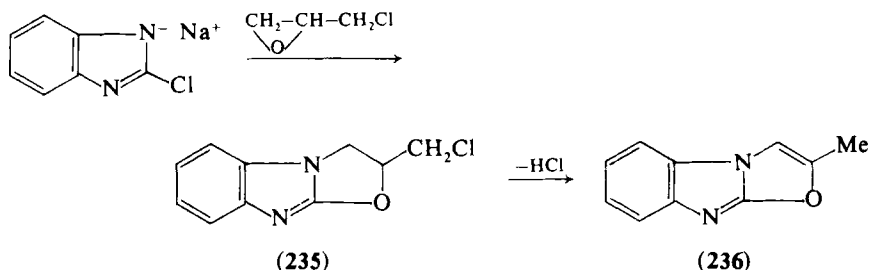
³⁰⁹ B. T. Heitke and C. G. McCarty, *Can. J. Chem.* **52**, 2861 (1974).

³¹⁰ (a) R. M. Acheson and M. S. Verlander, *J. Chem. Soc., Perkin Trans. 1*, 2348 (1973); (b) 430 (1974).

The imidazo[2,1-*a*]isoindole (**234**) has been prepared from 2-ethoxyisoindole as shown in Eq. (29).³¹¹



2-Methyloxazolo[3,2-*a*]benzimidazole (**236**), the first representative of a novel ring system, was recently prepared by reaction of the sodium salt of 2-chlorobenzimidazole with epichlorohydrin. Ring closure with loss of chloride ion gave the dihydro compound **235**, which aromatized to **236** on boiling with alkali.³¹²



4. Formation of Both Rings Simultaneously

a. *Condensation of 1,2-Diamines with 1,4-Dicarbonyl Compounds.* The reaction of aliphatic and aromatic diamines with 1,4-diketones, dialdehydes, ketoesters, or diesters has been used to prepare pyrrolo-[1,2-*a*]imidazoles,^{313a} pyrrolo[1,2-*a*]benzimidazoles,^{313-315a} imidazo[2,1-

³¹¹ R. G. Glushkov and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.* **1**, 85 (1965).

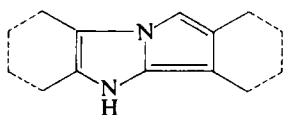
³¹² F. Benigni and L. Trevisan, *Farmaco Ed. Sci.* **29**, 936 (1974).

³¹³ (a) W. J. Houlihan (Sandoz Inc.), U.S. Patent 3,334,099 (1967) [*CA* **69**, 96769 (1968)]; (b) G. T. Tatevosyan and Z. V. Esayan, USSR Patent 449,054 (1974) [*CA* **82**, 57699 (1975)].

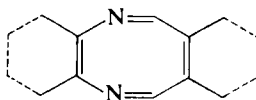
³¹⁴ W. Ried and G. Isenbruck, *Angew. Chem., Int. Ed. Engl.* **9**, 793 (1970).

³¹⁵ (a) W. W. Paudler and A. G. Zeiler, *J. Org. Chem.* **34**, 2138 (1969); (b) A. P. Bindra and J. A. Elix, *Tetrahedron* **26**, 3749 (1970); (c) J. L. Aubagnac, J. Elguero, and R. Robert, *Bull. Soc. Chim. Fr.*, 2868 (1972).

a]isoidoles,^{132, 316–320} and isoindolo[2,1-a]benzimidazoles.^{315, 321–324} In many cases either pyrrolo[1,2-a]imidazole derivatives (237) or diazocines (238) are isolated depending on the conditions.^{314, 315, 317–325}

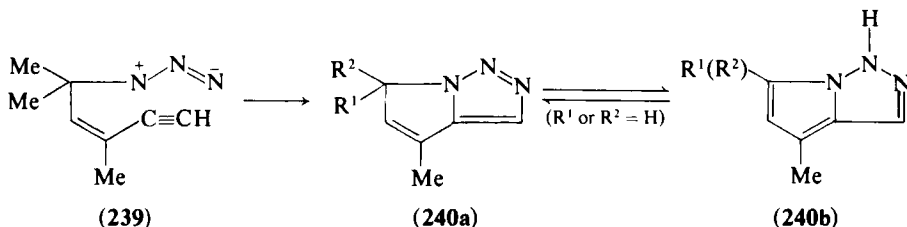


(237)



(238)

b. *Miscellaneous.* It is reported³²⁶ that the azide group in 239 undergoes 1,3-dipolar cycloaddition to the acetylenic bond to give the pyrrolo[1,2-c][1,2,3]triazole (240a). Recently³²⁷ the monosubstituted



a: $\text{R}^1 = \text{R}^2 = \text{Me}$

b: $\text{R}^1 \text{ or } \text{R}^2 = \text{H}$

³¹⁶ P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **34**, 165 (1969).

³¹⁷ (a) J. R. Geigy A.-G., Netherland Patent 6,613,264 (1967) [*CA* **67**, 82204 (1967)]; (b) J. R. Geigy A.-G., Belgium Patent 659,530 (1965) [*CA* **64**, 6664 (1966)].

³¹⁸ T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.* **32**, 2180 (1967).

³¹⁹ W. Metlesics, T. Anton, and L. H. Sternbach, *J. Org. Chem.* **32**, 2185 (1967).

³²⁰ W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.* **33**, 2874 (1968).

³²¹ (a) J. Robin, French Patent 1,090,115 (1955) [*CA* **53**, 8645 (1959)]; (b) H. N. Rydon, N. H. P. Smith, and D. Williams, *J. Chem. Soc.*, 1900 (1957); (c) J. Dassigny and J. Robin, French Patent 67,355 (1958) [*CA* **55**, 6875 (1961)]; (d) A. I. Kiprianov and V. A. Shrubovich, *Zh. Obshch. Khim.* **30**, 3746 (1960); (e) V. Anger, *Oesterr. Chem. Ztg.* **62**, 352 (1961); (f) F. Sparatore and G. Bignardi, *Gazz. Chim. Ital.* **92**, 606 (1962); (g) D. Amos and R. G. Gillis, *Aust. J. Chem.* **17**, 1440 (1964).

³²² W. G. Salmond, *Tetrahedron Lett.*, 4689 (1967).

³²³ (a) H. D. Perlmutter and P. S. Knapp, *J. Org. Chem.* **32**, 2350 (1967); (b) J. Arient and J. Marhan, *Collect. Czech. Chem. Commun.* **26**, 98 (1961); (c) J. Arient, L. Havlickova, and J. Slosar, *ibid.* **29**, 3115 (1964); (d) **30**, 1913 (1965); (e) G. Irick, *J. Heterocycl. Chem.* **7**, 33 (1970).

³²⁴ P. R. Young, *J. Heterocycl. Chem.* **9**, 371 (1972).

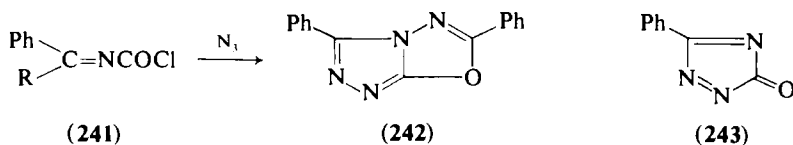
³²⁵ G. Adembri, S. Chimichi, F. De Sio, R. Nesi, and M. Scotton, *J. Chem. Soc., Perkin Trans. I*, 1022 (1974).

³²⁶ J. P. Dulcère, M. Santelli, and M. Bertrand, *C.R. Hebd. Seances Acad. Sci. Ser. C.* **271**, 585 (1970).

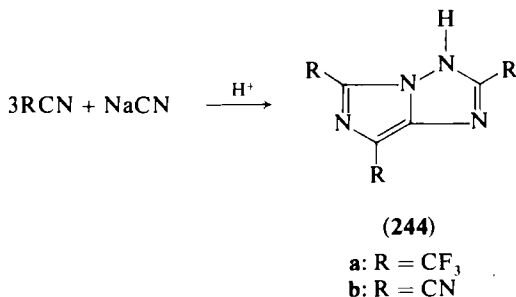
³²⁷ M. Bertrand, J. P. Dulcère, and M. Santelli, *Tetrahedron Lett.*, 1783 (1977).

analog **240b** has been prepared, but like other pyrroloazoles (Section IV,A,1, Scheme 10) the most stable tautomer has structure **240a** (R^1 or $R^2 = H$).

N-(α -Chlorobenzylidene)carbamoyl chloride (**241**; $R = Cl$) reacted with sodium azide in glyme to give the fused oxadiazole **242** in 52% yield, in addition to other products.³²⁸ The mechanism of this reaction is uncertain, but it is thought to involve the intermediacy of **241** ($R = N_3$) and the triazolone **243**.



Imidazo[1,5-*b*]-*s*-triazoles (**224a, b**) result from treatment of trifluoroacetonitrile³²⁹ or cyanogen³³⁰ with sodium cyanide. The mechanism involves attack of cyanide ion on RCN, followed by addition to further RCN molecules, then ring-closure. The structure of **244a** was confirmed by spectroscopic methods.³²⁹



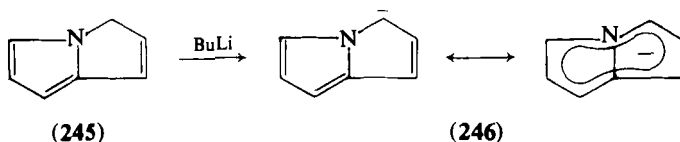
5. Synthesis by Deprotonation

Okamura and Katz³¹ prepared the azapentalenyl ion **246** in solution by treatment of the dihydro compound **245** with *n*-butyllithium at -78° (cf. Section III,A,5). The spectroscopic properties and chemistry of this ion have been extensively explored, and the UV spectrum closely resembles that of the pentalenyl dianion² (Section I).

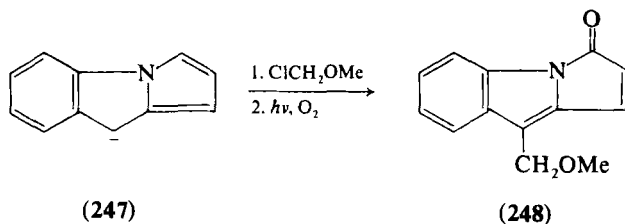
³²⁸ O. Tsuge, M. Yoshida, and S. Kanemasa, *J. Org. Chem.* **39**, 1226 (1974).

³²⁹ W. J. Middleton and D. Metzger, *J. Org. Chem.* **35**, 3985 (1970).

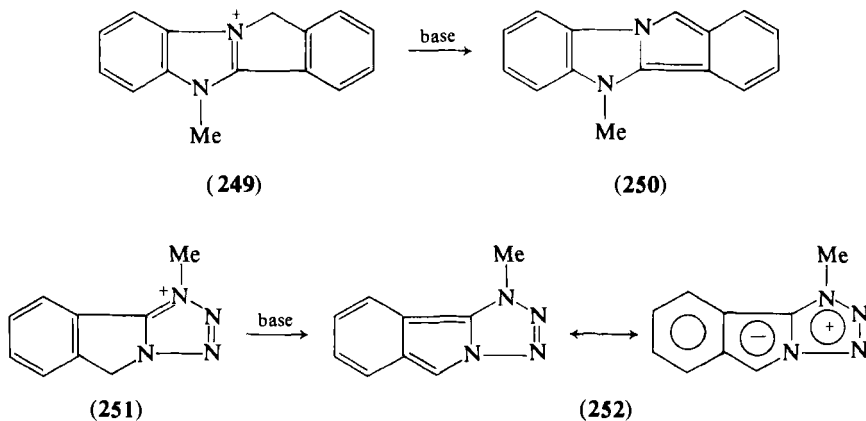
³³⁰ F. S. Babichev, L. G. Khil'ko, and N. V. Mel'nichenko, *Ukr. Khim. Zh.* **35**, 615 (1969) [*CA* **71**, 70538 (1969)].



More recently Franck *et al.*³³¹ prepared the pyrrolo[1,2-*a*]indolyl anion (247) by a similar method as part of a total synthesis of the mitomycin antibiotics (Section VI,A). Alkylation of (247) with methyl chloromethyl ether followed by photooxidation gave a product 248 with the basic mitomycin skeleton.



Deprotonation of the quaternary salts 249 and 251 is reported to give the isoindolobenzimidazole 250³³⁰ and the tetrazoloisoindole 252,³³² respectively. These products are related to the indenopyrazoles of type A mentioned earlier (Section III,A,5).



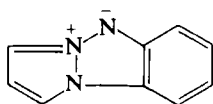
³³¹ G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.* **39**, 3739 (1974).

³³² F. S. Babichev and N. N. Romanov, *Ukr. Khim. Zh.* **39**, 49 (1973) [*CA* **78**, 111229 (1973)].

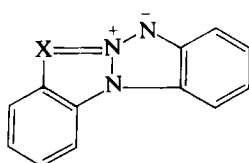
C. AZAPENTALENES WITH TWO RING JUNCTION NITROGEN ATOMS (TYPE C)

1. [5 + 0] Syntheses

a. *Intramolecular Cyclization of Nitrene Intermediates.* Various systems have been obtained by cyclization of nitrenes generated from nitro compounds with TEP. 1-(*o*-Nitrophenyl)pyrazoles yield pyrazolo-[1,2-*a*]benzotriazoles (**253**),^{333, 334a} and 1-(*o*-nitrophenyl)-1*H*-indazoles give indazolo[1,2-*a*]benzotriazoles (**254a**)³³⁵ under these conditions. Derivatives of **253** have recently been obtained from 2-(*o*-nitrophenyl)-2*H*-indazoles.^{334b} The tetraazapentalenes **255** and **254b** were obtained in

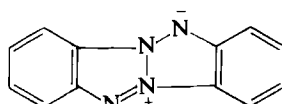


(253)



(254)

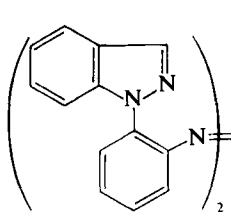
a: X = CH
b: X = N



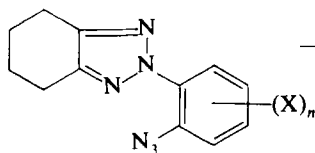
(255)

the same way from 2-(*o*-nitrophenyl)benzotriazole³³⁶ and 1-(*o*-nitrophenyl)benzotriazole,^{336, 337} respectively.

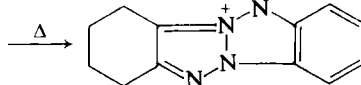
Photolytically generated nitrene derived from 1-(*o*-azidophenyl)-1*H*-



(256)



(257)



(258)

³³³ (a) B. M. Lynch and Y. Y. Hung, *J. Heterocycl. Chem.* **2**, 218 (1965); (b) O. Meth-Cohn, *Lakeland Meeting Heterocycl. Chem. Group*, 2nd, 12 (1975); I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Lett.*, 925 (1976).

³³⁴ (a) R. J. Harder and J. C. Kauer (E. I. du Pont de Nemours and Co.), U.S. Patent 3,262,944 (1966) [*CA* **65**, 13726 (1966)]; (b) A. J. Nunn and F. J. Rowell, *J. Chem. Soc., Perkin Trans. 1*, 629 (1975).

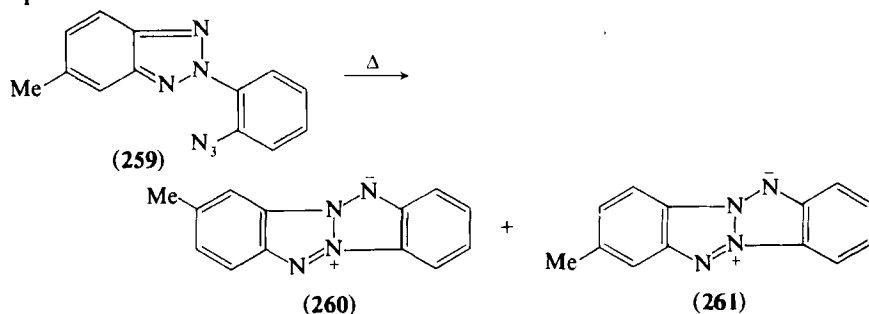
³³⁵ O. Tsuge and H. Samura, *J. Heterocycl. Chem.* **8**, 707 (1971).

³³⁶ J. C. Kauer and R. A. Carboni, *J. Am. Chem. Soc.* **89**, 2633 (1967).

³³⁷ J. C. Kauer (E. I. du Pont de Nemours and Co.), U.S. Patent 3,262,943 (1966) [*CA* **65**, 13726 (1966)].

indazole cyclized to give **254a** (23% yield) plus the dimer **256** (10% yield). Thermolysis of the azido compound **257** gave the tetraazapentalene **258**.³³⁸

Other tetraazapentalenes have been produced by photochemical or thermal decomposition of azidophenyl-1*H*- and -2*H*-benzotriazoles.^{339–341} Hall, Stephanie, and Nordstrom³⁴¹ found that decomposition of the azide **259** in decalin at 170° led to a mixture of **260** and **261** in the ratio 1:9. The preference for cyclization to the position para to the methyl group to give **261** is consistent with the known electrophilic character of the intermediate nitrene.



b. *Other Cyclization Methods.* Substituted pyrazolo[1,2-*a*]pyrazoles (**262**, R = COAr) were prepared^{342, 343} from quaternary pyrazolium salts using Tschitschibabin's method [Eq. (30)] (see Section III,B,3,b). More recently, various workers^{344–349} have introduced a new route to this system, illustrated by synthesis of the parent compound [Eq. (31)]. Bromination of 1-allylpyrazole followed by thermal quaternization and deprotonation gave the unstable pyrazolo[1,2-*a*]pyrazole (**262**, R = H) which was characterized chemically and by spectroscopy.³⁴⁴ More stable substituted derivatives have been obtained by this route.^{345–349}

³³⁸ R. A. Carboni (E. I. du Pont de Nemours and Co.), U.S. Patent 3,262,942 (1966) [CA 65, 15556 (1966)].

³³⁹ R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Am. Chem. Soc.* **89**, 2618 (1967).

³⁴⁰ R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *J. Am. Chem. Soc.* **89**, 2626 (1967).

³⁴¹ J. H. Hall, J. G. Stephanie, and D. K. Nordstrom, *J. Org. Chem.* **33**, 2951 (1968).

³⁴² T. W. G. Solomons and F. W. Fowler, *Chem. Ind. (London)*, 1462 (1963).

³⁴³ T. W. G. Solomons, F. W. Fowler and J. Calderazzo, *J. Am. Chem. Soc.* **87**, 528 (1965).

³⁴⁴ S. Trofimenko, *J. Am. Chem. Soc.* **87**, 4393 (1965).

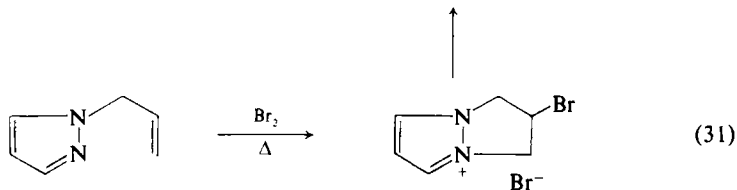
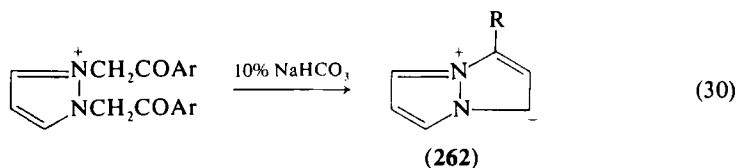
³⁴⁵ T. W. G. Solomons and C. F. Voigt, *J. Am. Chem. Soc.* **87**, 5256 (1965).

³⁴⁶ T. W. G. Solomons and C. F. Voigt, *J. Am. Chem. Soc.* **88**, 1992 (1966).

³⁴⁷ S. Trofimenko, *J. Am. Chem. Soc.* **88**, 5588 (1966).

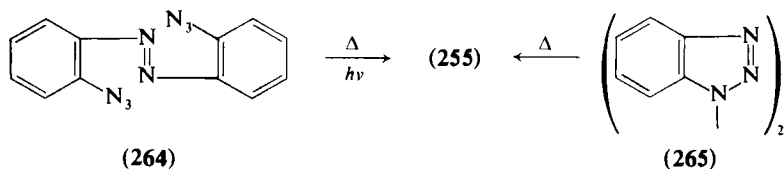
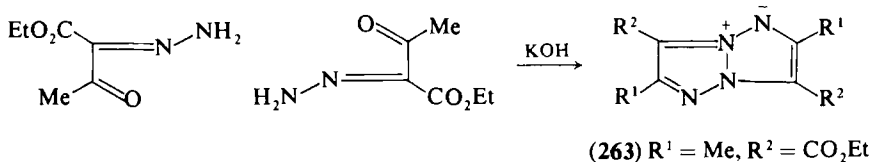
³⁴⁸ R. J. Harder, R. A. Carboni, and J. E. Castle, *J. Am. Chem. Soc.* **89**, 2643 (1967).

³⁴⁹ S. Trofimenko (E. I. du Pont de Nemours and Co.), U.S. Patent 3,431,275 (1969) [CA 71, 62290 (1969)].



2. Formation of Both Rings Simultaneously

Several tetraazapentalenes and one triazapentalene have been obtained by specific cyclization reactions. Potassium hydroxide in methanol effected condensation of two molecules of ethyl acetylglyoxylate α -hydrazone to give **263**, and this synthesis has been applied to the preparation of other derivatives.^{350–353} Thermal or photochemical decomposition of **264** produces **255** via the dinitrene,^{339,354} and cyclization of a similar nitrene derived from **267** with TEP gives the triazapentalene **268**.⁶² Loss of nitrogen from the dibenzotriazolyls **265** and **266** on heating affords the tetraazapentalenes **255** and **254b**, respectively, in fair yield.³⁴⁸



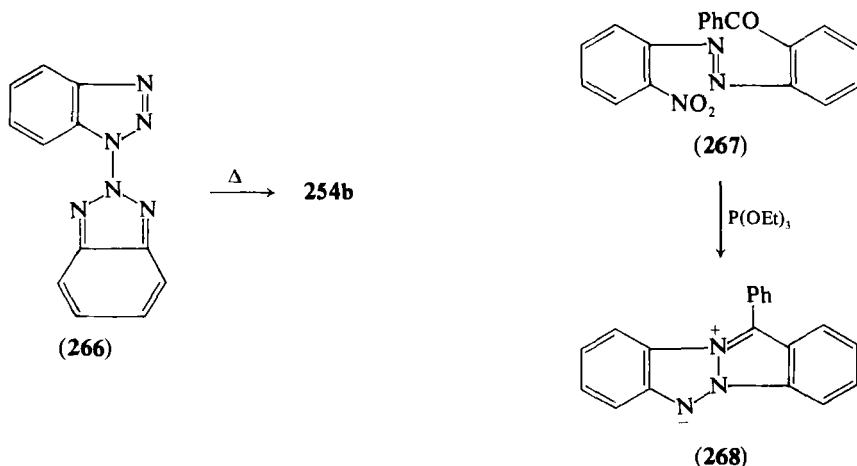
³⁵⁰ R. Pflieger, E. Garthe, and K. Rauer, *Chem. Ber.* **96**, 1827 (1963).

³⁵¹ M. Brufani, W. Fedeli, G. Giacomello, and A. Vaciago, *Chem. Ber.* **96**, 1840 (1963).

³⁵² R. Pflieger, E. Garthe, and K. Rauer, German Patent 1,245,386 (1967) [*CA* **68**, 69005 (1968)].

³⁵³ R. Pflieger, E. Garthe, and K. Rauer, German Patent 1,620,103 (1971) [*CA* **75**, 49090 (1971)].

³⁵⁴ R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.* **84**, 2453 (1962).



D. GENERAL REMARKS

The last five years have seen an enormous upsurge of interest in aromatic azapentalenes, particularly by Russian and Japanese workers, and this is reflected in the large number of new syntheses that have appeared during this period. Many of the reactions of the foregoing section are simply extensions of standard procedures for preparing five-membered ring monocycles, though it is perhaps interesting that relatively few new systems containing oxygen as a heteroatom have been reported. Most work has been devoted to systems of type B, and type C azapentalenes have received the least attention. Certain unexpected difficulties encountered in applying particular methods to the synthesis of aromatic azapentalenes have been discussed in the text, particularly with regard to the Tschitschibabin reaction (Section III,B,3,a) and 1,3-dipolar cycloadditions (III,B,3,c).

A general method of potential synthetic usefulness is the preparation of aromatic azapentalenes by oxidation of partially saturated systems. This has been used with success in a few cases (e.g., Sections III,A,3,d,^{108, 109} III,B,3,c,²⁹³⁻²⁹⁵ III,A,2⁸⁴), but it has not been extensively explored. Recently, several workers have reported some possibly significant failures while attempting the dehydrogenation of non-aromatic systems. Various 2,3-dihydroimidazo[1,2-b]pyrazoles resisted oxidation to the corresponding aromatic system with manganese dioxide, chloranil, or dicyanodichloroquinone (DDQ),³⁵⁵ and a

³⁵⁵ J. Elguero, L. Knutsson, and S. Mignonac-Mondon, *Bull. Soc. Chim. Fr.*, 255 (1975).

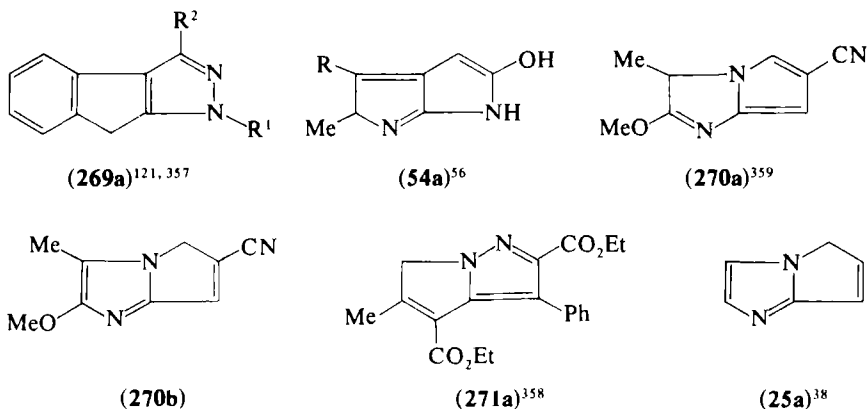
derivative of 2,3-dihydroimidazo[1,2-*a*]imidazole also failed to undergo oxidation with manganese dioxide. In this last case a dimeric product was isolated.²¹² More work is clearly necessary before the reasons for these failures are known.

IV. Reactivity

A. TAUTOMERISM

1. Annular Tautomerism

Exchange of a proton between atoms forming part of the heterocyclic ring in a heteroaromatic system is known as annular tautomerism. This phenomenon is characteristic of pyrroles and aza derivatives (azoles) unsubstituted on nitrogen,³⁵⁶ and it is therefore seen also in azapentalenes possessing at least one NH group. Among aromatic azapentalenes, two main types of tautomers can be distinguished: nonaromatic CH structures (e.g., **275a**) and aromatic NH forms (e.g., **275b**). CH tautomers appear to be stable only in systems where one of the azapentalene rings is pyrrole or cyclopentadiene; some examples are shown in Scheme 10. In some cases where more than one CH tautomer is possible, structures have not been established with certainty. For example, the pyrrolo[1,2-*a*]imidazole **270** is reported³⁵⁹ to exist as **270a**, but no evidence is presented to exclude the alternative structure **270b**.

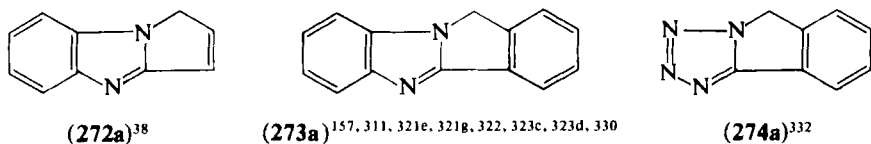


³⁵⁶ J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles," p. 266. Academic Press, New York, 1976.

³⁵⁷ K. Hartke and W. Uhde, *Chem. Ber.* **103**, 2667 (1970).

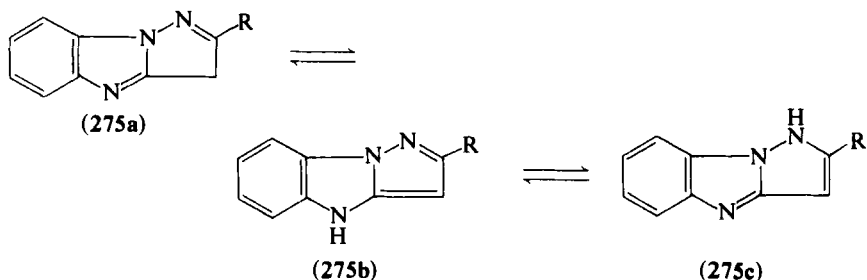
³⁵⁸ A. Morimoto and H. Takasugi, Japanese Patent 7,131,548 (1971) [*CA* **76**, 3851 (1972)].

³⁵⁹ C. A. Grob and P. Ankli, *Helv. Chim. Acta* **33**, 273 (1950).

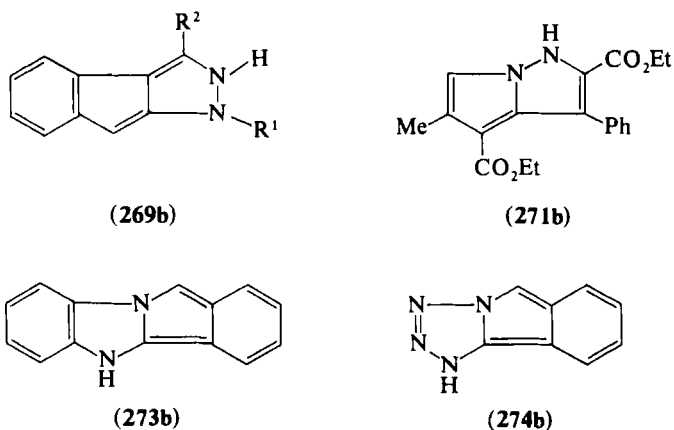


SCHEME 10

When both rings in azapentalenes have more than one nitrogen atom, the CH tautomer is unstable; thus structure **275a**, proposed by some workers,¹⁴⁸ is unlikely, and the compound is better represented by the NH forms **275b** or **275c**. The factors that influence the relative stabilities of NH tautomers are more complex and can be summarized in four "rules":



i. The presence of two adjacent heteroatoms, each contributing a doublet to the π -system, is energetically unfavorable.^{268b, 360} This explains why the 10- π NH tautomers, e.g., **269b** and **271b**, exist in the CH forms **269a** and **271a**, respectively.

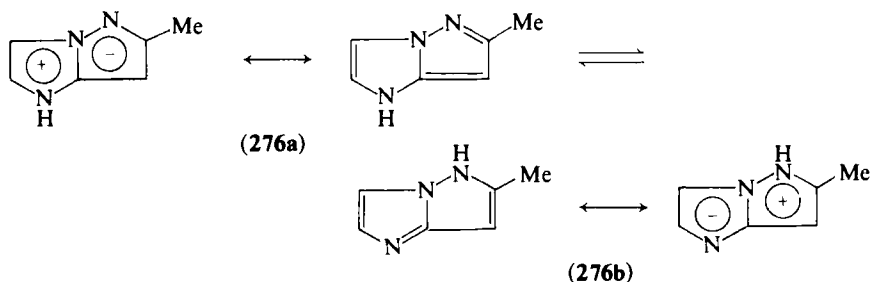


³⁶⁰ J. P. Fayet, M. C. Vertut, R. M. Claramunt, J. M. Fabregà, and L. Knutsson, *Bull. Soc. Chim. Fr.*, 393 (1975).

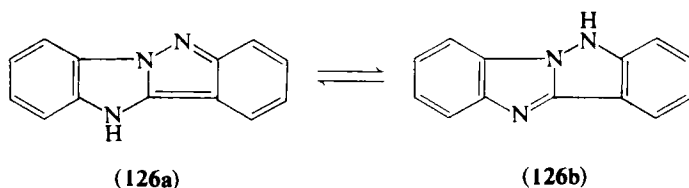
ii. Peri-interactions from lone pairs that lie in the plane of the molecule but do not contribute to the π -system (i.e., from pyridinoid nitrogen,³⁶¹ furan-type oxygen, and thiophene-type sulfur) destabilize the system.

iii. Benzenoid systems are more stable than quinonoid forms; this accounts for the destabilization of structures such as **273b** and **274b**.

iv. The five-membered ring that carries the tautomerizable hydrogen will be π -electron deficient and the other ring π -electron excessive (e.g. **276**), and thus the tautomer that carries the positive charge in the more "basic" ring and the negative charge in the more "acidic" ring will be the most stable. Since basicity increases and acidity decreases along the series tetrazole, *v*-triazole, *s*-triazole, pyrazole, imidazole, tautomer **276a** should be more stable than **276b**.



Usually, these "rules" operate in the same sense, though cases are known where they oppose each other. For example, since there are no data on the equilibrium **126a** \rightleftharpoons **126b**,^{123b} it is not possible to predict which factors predominate. For some systems the position of equilibrium has been studied by physical methods, and these will be discussed in the light of the four "rules" above.



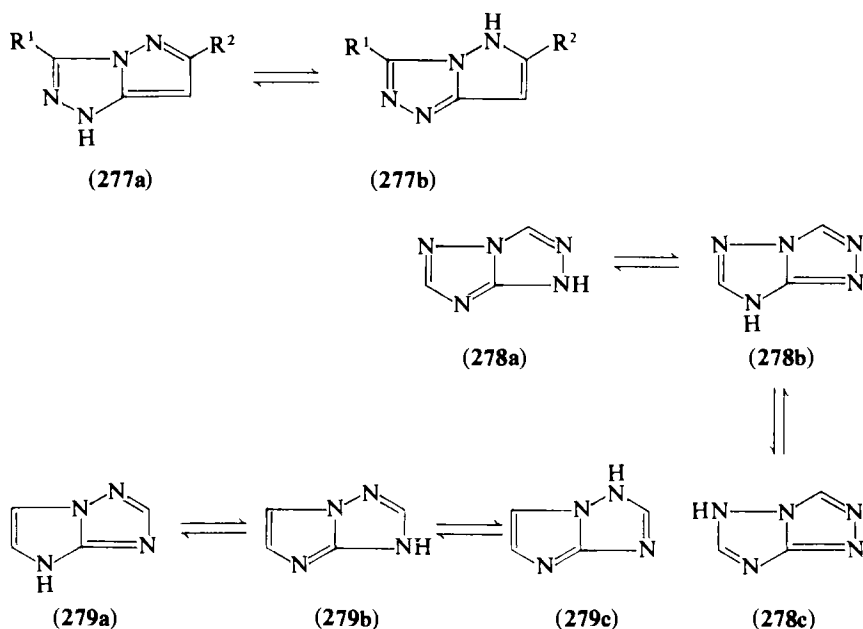
The use of NH coupling in proton magnetic resonance PMR spectroscopy (Section V,G,2) and dipole moment measurements has enabled the greater stability of **275b** over **275c**^{362, 363} and **276a** over

³⁶¹ J. A. Zoltewicz and A. A. Sale, *J. Am. Chem. Soc.* **95**, 3928 (1973).

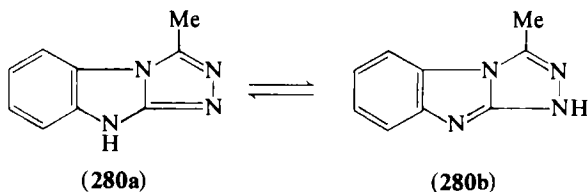
³⁶² J. Elguero, A. Fruchier, L. Knutsson, R. Lazaro, and J. Sandström, *Can. J. Chem.* **52**, 2744 (1974).

³⁶³ J. P. Fayet, M. C. Vertut, P. Mauret, J. de Mendoza, and J. Elguero, *J. Heterocycl. Chem.* **12**, 197 (1975).

276b^{245, 360, 362} to be demonstrated. These results are accounted for by rules i and ii. The greater stabilities of **277a**³⁶⁰ and **278a**³⁶⁴ have been shown by dipole moment studies, and the destabilization of **277b** suggests that rule i predominates over rule iv. Although a combination of rules i and ii account for the lower stability of **278c**, the greater stability of **278a** over **278b** is not explained so easily. Among imidazo-[1,2-*b*]-*s*-triazoles (**279**),^{268b} NMR studies have revealed that **279a** predominates, favored by rule iv, whereas the destabilization of **279c** is accounted for by rules i and ii.



The position of equilibrium in **280** is solvent dependent;^{195, 363, 365} UV and dipole moment studies show that **280a** predominates in ethanol, and **280b** in dioxane.

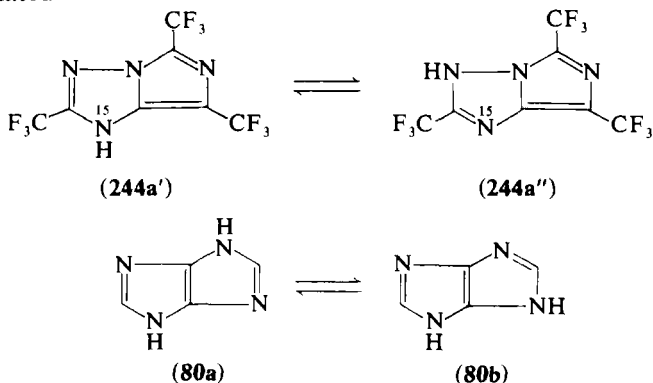


³⁶⁴ R. M. Claramunt, J. P. Fayet, M. C. Vertut, P. Mauret, and J. Elguero, *Tetrahedron* **31**, 545 (1975).

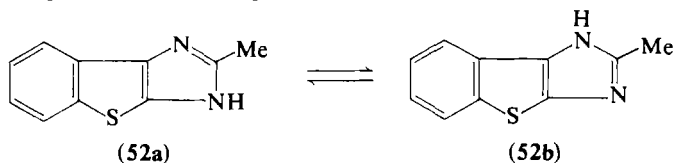
³⁶⁵ J. de Mendoza and M. C. Pardo, *An. Quim.* **71**, 434 (1975).

Two results in the literature appear at first sight to violate rules i–iv. In the PMR spectrum of **277** ($R^1 = R^2 = H$), the “ortho” coupling constant between the pyrazole ring protons was found to be 2.3 Hz in dimethyl sulfoxide (DMSO).²⁰⁷ This high value, suggesting considerable double-bond character between the pyrazole carbon atoms, led the authors²⁰⁷ to conclude that **277b** predominated in DMSO. The synthesis of **308** ($R^1 = R^2 = H$) (Section IV,B,1), an aza derivative of **277a**, showed that the coupling constant in systems of this type could be as high as 2.4 Hz,³⁶⁶ and this abnormally high value is indicative of the localized nature of the azapentalene π -system (Section VII).

In the spectrum of **244a**, the absence of 1H – ^{15}N coupling, even in acetone at -120° , and the width of the NH signal, suggested that **244a''** predominates.³²⁹ However, the use of negative arguments requires caution, and it seems possible that **244a'** is not definitely excluded, nor rule i violated.

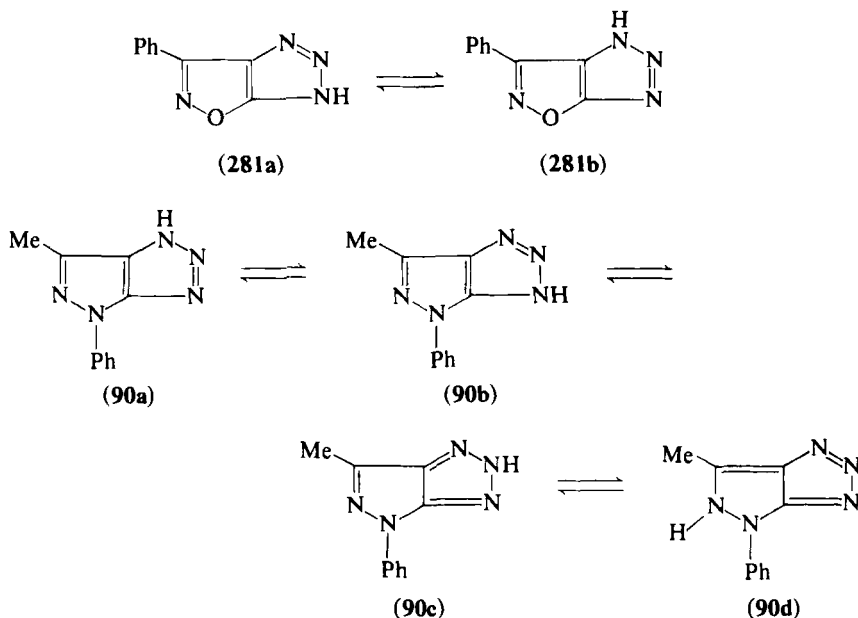


For azapentalenes of type A (e.g. **80**,^{73b} **52**,⁵⁵ and **281**⁶⁰), rule ii should favor the **a'** structure shown in each case. Unfortunately, the position of equilibrium in these compounds has not been measured. A rare case where the annular tautomerism of a type A azapentalene has been investigated is the pyrazolo[3,4-*d*]-*v*-triazole **90**. Although results from dipole moment measurements were inconclusive, it is likely that **90a** and **90c** predominate at equilibrium.³⁶⁷

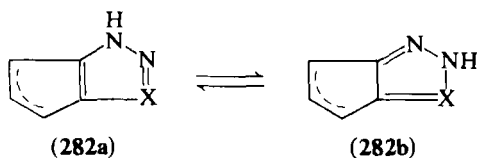


³⁶⁶ E. Alcalde and R. M. Claramunt, *J. Heterocycl. Chem.*, **13**, 379 (1976); R. M. Claramunt, J. Elguero, A. Fruchier, and M. J. Nye, *Afinidad*, in press.

³⁶⁷ M. C. Vertut, J. P. Fayet, E. Gonzalez, R. Sarlin, and J. Elguero, *Bull. Soc. Chim. Fr.*, 1871 (1975).



Many fused pyrazoles of general type **282** ($X = CR$) have been prepared,^{53, 65, 112, 368} but no indication of the position of equilibrium **282a** \rightleftharpoons **282b** is reported, and it would be interesting to know whether rule iii plays a part in determining the stability of these structures. Results obtained from studies on acetylated derivatives of **282** (Section IV,C,3) and on **90** suggest that the energy difference between **282a** and **282b** is less than that between benzenoid and quinonoid structures.



It is possible to approach the problem of annular tautomerism using semiempirical quantum-mechanical calculations (Section V,B): the results are in accord with the empirical rules used in this section.

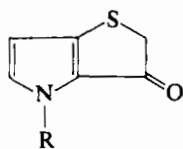
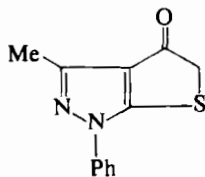
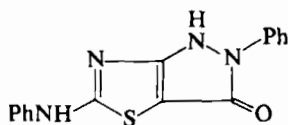
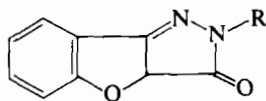
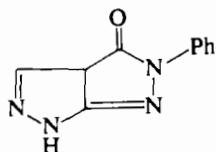
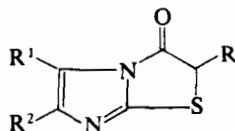
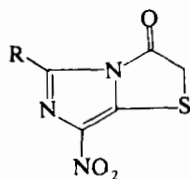
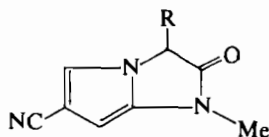
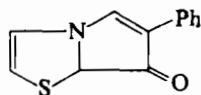
2. Functional Tautomerism

Although many azapentalenes have OH, SH, or NH₂ substituents, there are few studies of their tautomerism. Nevertheless, as a general

³⁶⁸ I. I. Grandberg, S. V. Tabak, N. I. Bobrova, A. N. Kost, and L. G. Vasina, *Khim. Geterotsikl. Soedin.* **1**, 407 (1965).

rule nonaromatic tautomers, particularly oxo structures, are more stable than their counterparts in monocyclic azoles,³⁵⁶ an indication of the lower aromaticity of azapentalenes with respect to monocyclic systems (Section VII).

a. *Oxo-Hydroxy*. In all compounds where the structure of the tautomer has been established with certainty, the oxo form has been found exclusively, whether in solution or the solid state. The same situation probably obtains in most other cases, and it therefore seems more accurate to write all compounds in this form for the time being. Scheme 11 shows examples of some systems; where the structure has been determined, the physical method used is indicated.

(26) (NMR, IR)^{39, 369}(283) (UV, IR, NMR)⁹⁵(284) (X-ray)³⁷⁰(285) (IR)¹⁰⁰(286)³⁷¹(287)^{223c, 251, 373} (IR)²⁵²(288) (IR)^{247d}(289) (IR)³⁵⁹(290)^{271b}

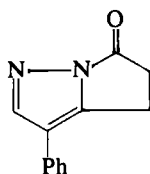
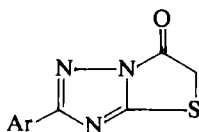
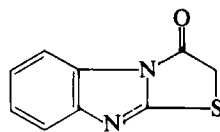
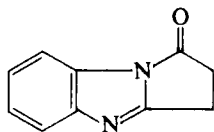
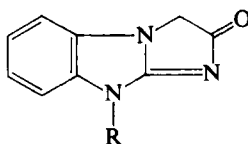
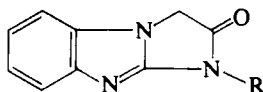
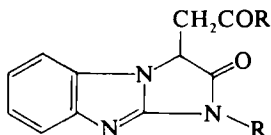
³⁶⁹ W. Carpenter and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2592 (1960).

³⁷⁰ D. L. Smith, *Acta Crystallogr., Ser. B* **25**, 625 (1969).

³⁷¹ H. Bredereck, F. Effenberger, and W. Resemann, *Chem. Ber.* **95**, 2796 (1962).

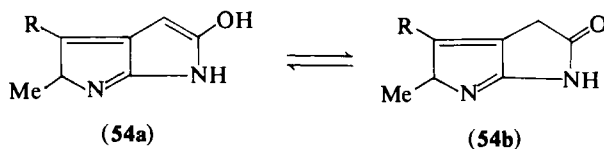
³⁷² T. A. Borisova, A. M. Simonov, and V. A. Anisimova, *Khim. Geterotsikl. Soedin.* **9**, 803 (1973).

³⁷³ M. I. Ali, M. A. Abou-State, and A. F. Ibrahim, *J. Prakt. Chem.* **316**, 147 (1974).

(291) (IR)³⁷⁴(292) (IR, NMR)³⁷⁵(293a)³⁰⁰ (IR, NMR)^{152a, 262a, 262b, 257}(293b) (IR, NMR)^{315c}(161a)³⁷²(161b)³⁷²(170) (IR)¹⁶⁰

SCHEME 11

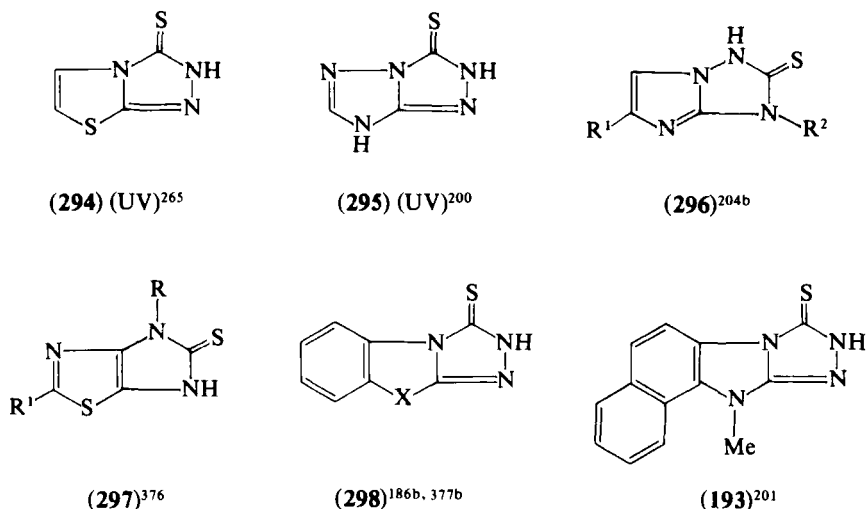
The only compound in which the hydroxy form has been demonstrated is **54**, which exists as **54a** (Scheme 10) in DMSO (shown by NMR) and **54b** in the solid state (shown by IR).⁵⁶



b. *Thione–Thiol*. UV measurements on **294** and **295** (Scheme 12) have shown that the thione form exists in solution. Although the other systems have not been studied, it seems reasonable to represent them in the thione form.

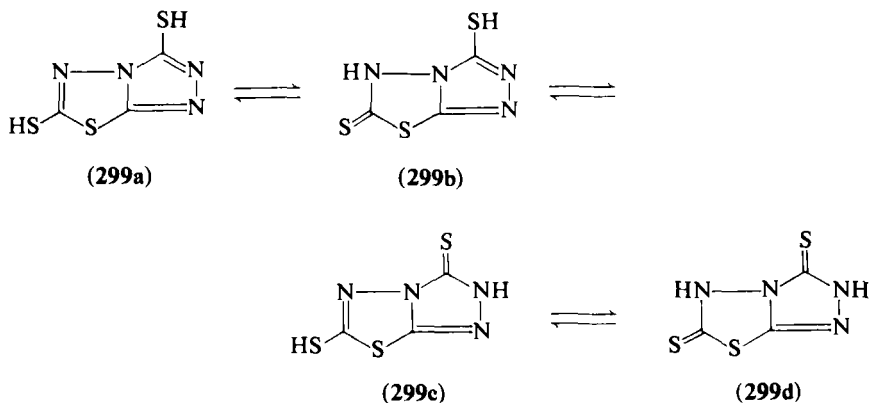
³⁷⁴ A. Morimoto, K. Noda, T. Watanabe, and K. Takasugi, *Tetrahedron Lett.*, 5707 (1968).

³⁷⁵ A. Abd-El-Wahid Soliman, Ph.D. Thesis, Giza, Egypt (1972).



SCHEME 12

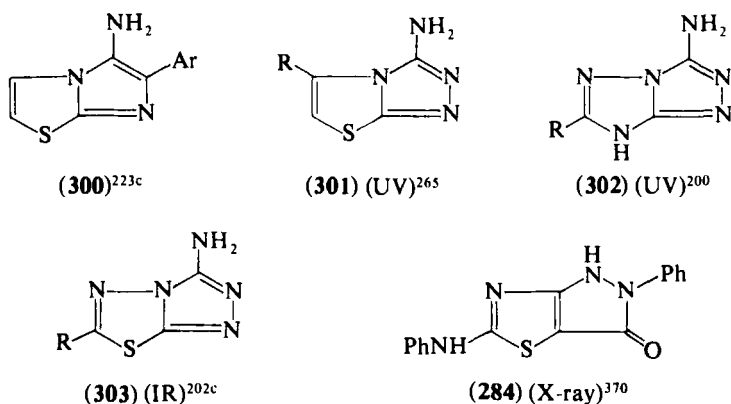
Studies on the bifunctional compound **299** in dioxane (by UV) and in the solid state (by IR) show that **299c** is the most stable tautomer. This result has been supported by MO calculations.^{377a}



c. *Amine-Imine*. For the systems studied (Scheme 13), physical methods have shown the amine structure to be stable, as in monocyclic azoles.³⁵⁶

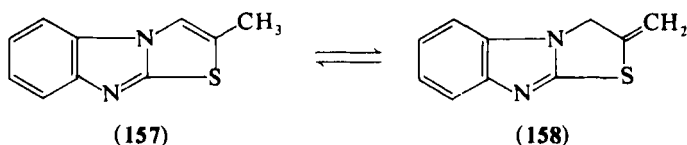
³⁷⁶ B. Dash and S. K. Mahapatra, *Current Sci.* **39**, 559 (1970).

³⁷⁷ (a) E. G. Kovalev, A. D. Sinigibskaya, I. Y. Postovsky, and S. L. Mertsalov, *Khim. Geterotsikl. Soedin.* **11**, 349 (1975); (b) N. P. Bednyagina and I. N. Getsova, *Zh. Org. Khim.* **1**, 139 (1965).



SCHEME 13

d. *Methyl-Methylene*. Normally, alkyl groups are not dealt with when tautomerism is discussed since the aromatic tautomer is very largely predominant. It is therefore remarkable that the two compounds **157** and **158** have been isolated,¹⁵⁵ though the former is more stable, as demonstrated by the fact that **158** is converted into **157** with sodium ethoxide. The ethyl analog behaves similarly, and in this respect it resembles 2-ethylthiophene rather than the corresponding thiazole.³⁵⁶



B. ISOMERISM

1. Azide-Tetrazole

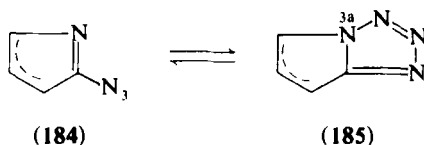
This topic has recently been comprehensively dealt with in several reviews^{190b, c, 378-380} and in a book on azide chemistry.³⁸¹ Here, we shall consider only aromatic systems **184** that assume an azapentalene structure **185** in the tetrazole form.

³⁷⁸ M. Tišler, *Synthesis*, 123 (1973).

³⁷⁹ E. Alcalde and J. de Mendoza, in E. Alcalde, Ph.D Thesis, Barcelona, Spain (1974).

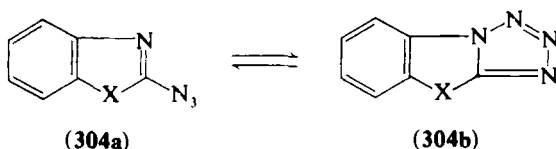
³⁸⁰ V. Y. Pochinok, L. F. Avramenko, T. F. Grigorenko, and V. N. Skopenko, *Russ. Chem. Rev.* **44**, 481 (1975).

³⁸¹ S. Patai, "The Chemistry of the Azido Group." Wiley (Interscience), New York, 1971.

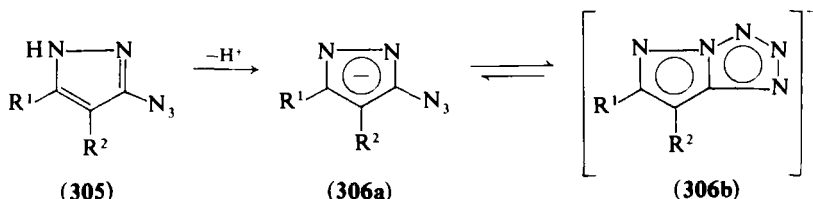


The position of this equilibrium depends on four factors, which we shall consider in turn: (i) the heteroatom that contributes a doublet to the π -system; (ii) the substituents (including the influence of pyridinoid nitrogen atoms); (iii) the state of the substance (solid or solution), and in the latter case, the solvent; (iv) the temperature.

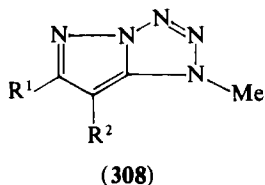
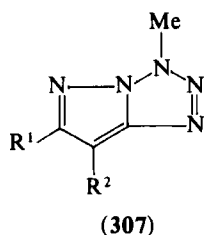
i. The nature of the heteroatom can play an important part. Reynolds *et al.*^{185a} investigated a series of 1,3-benzazoles **304** and found that the tetrazole form **304b** was stable when $X = S$ or Se , whereas the azide **304a** predominated when $X = NH$, O , or SO_2 . When $X = CH_2$, the tetrazole form should be stable, but the compound would not be completely aromatic.



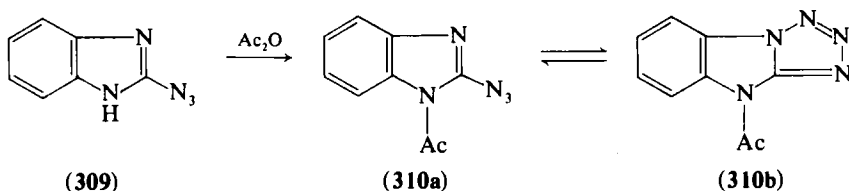
Other studies (see, e.g., ref. 187c and references cited therein) have revealed that, in systems containing only O and N as heteroatoms, the azide form **184** is usually the only isomer observable in solution or in the solid state, whatever the position of the heteroatoms. Recent work has shown that the tetrazole forms are predominant in systems containing only nitrogen as the heteroatom in two special cases. If a proton is removed from the azide (e.g., **305**), the anion **306** cyclizes to the tetrazole **306b**.^{187b, 187c} The cyclized form is likewise formed from the anions of azido-indazoles,³⁶⁶ -imidazoles,^{186d} and -benzimidazoles^{186d} but cyclization is only partial with *s*-triazoles and negligible with tetrazoles.³⁶⁶ It is possible to "trap" the cyclized anions (e.g., **306b**) by methylation^{366, 382} (Section IV,C,2) and obtain stable pyrazolo[1,5-*d*]tetrazoles, **307** and **308**.



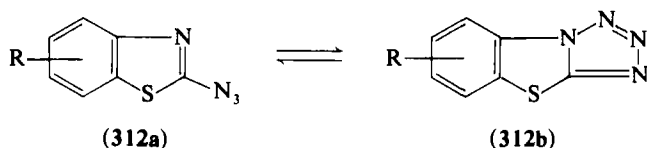
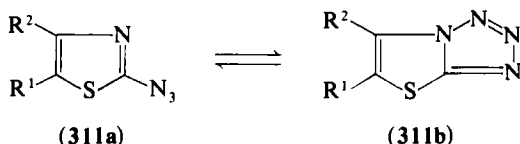
³⁸² E. Alcalde and R. M. Claramunt, *J. Heterocycl. Chem.* **13**, 379 (1976).



A strongly electron-attracting N-substituent (e.g., acetyl or formyl) stabilizes the tetrazole form; thus acetylation of 2-azidobenzimidazole (**309**) gives the tetrazole **310b**.^{186d}



ii. The effect of electron-attracting or donating substituents and pyridinoid nitrogen atoms has been extensively studied in azidoazines,^{378–381} but less frequently in azidoazoles. Studies on 2-azidothiazoles **311** and 2-azidobenzothiazoles **312**^{185b, 189a, 189b, 307, 383} have shown that electron-donating substituents favor the tetrazole form and electron-attracting groups favor the azide.



iii. In the solid state, IR determinations (for X-ray structures, see refs. 384, 385) have shown that the tetrazole is usually favored for thiazoles **311**^{189b} and benzothiazoles **312**.^{189a, 307a, 386} Solvents also play

³⁸³ R. Faure, J. P. Galy, G. Giusti, E. J. Vincent, and J. Elguero, *Org. Magn. Reson.* **6**, 485 (1974).

³⁸⁴ P. Domiano and A. Musatti, *Cryst. Struct. Commun.* **3**, 713 (1974).

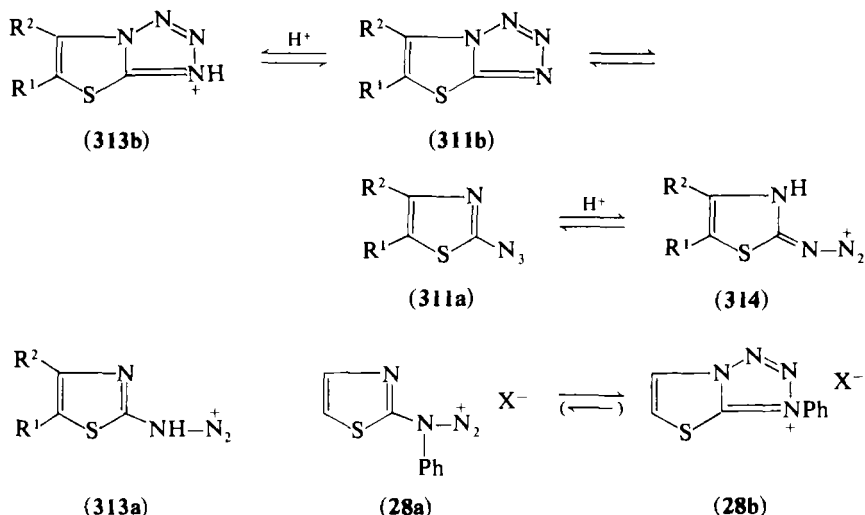
³⁸⁵ P. Domiano and A. Musatti, *Cryst. Struct. Commun.* **3**, 335 (1974).

³⁸⁶ J. H. Boyer and E. J. Miller, *J. Am. Chem. Soc.* **81**, 4671 (1959).

an important part, since the tetrazole form is favored in more polar and in basic media.^{307b} Nevertheless, even in DMSO and HMPT, no observable quantity of the tetrazole forms of **305** and **309** could be detected.³⁶⁶ In carbon tetrachloride, the thiazole **311** ($R^1 = R^2 = H$) exists entirely as the azide.^{307b}

iv. Since opening of the tetrazole ring (i.e., **185** \rightarrow **184**) involves an entropy increase of approximately $10 \text{ cal} \cdot \text{mol}^{-1} \text{ deg}^{-1}$,³⁷⁹ the cyclic isomer **185** should be more stable at low temperatures. This has been confirmed for thiazoles **311**,^{185b} benzothiazoles **312**,^{189a} and 1-acetyl-2-azidoimidazole.^{186d}

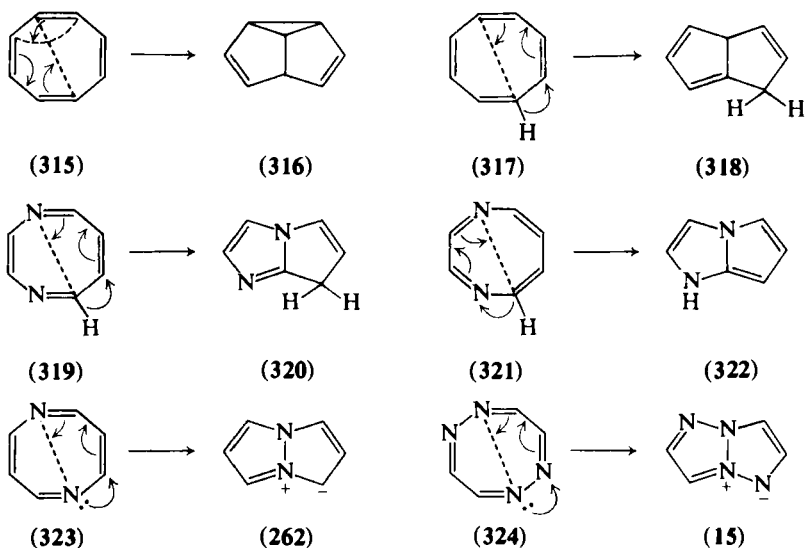
In trifluoroacetic acid, thiazolo[3,2-*d*]tetrazoles **311b** are protonated, and in this form opening to the azide **314** occurs very slowly.^{185b, 307} Nevertheless, when equilibrium is attained, it is the azide that predominates. It is likely that the small amount of free base **311b** present isomerizes to **311a**, which is then protonated, although direct isomerization **313b** \rightarrow **313a**, followed by prototropy (**313a** \rightarrow **314**) cannot be excluded. An argument against this second mechanism is the fact that, for **28**, the equilibrium is totally displaced toward the cyclic form **28b**.⁴¹



2. Ring Transformations

In Sections III,A,4 and III,B,1,f, examples of ring transformation reactions have been mentioned. Here we shall discuss in detail the interesting case of isomerism between an eight-membered ring with an $8-\pi$ -electron system (thus, in principle, antiaromatic) and a $10-\pi$ pentalene derivative (briefly mentioned in Section III,B,4,a). Scheme 14 shows

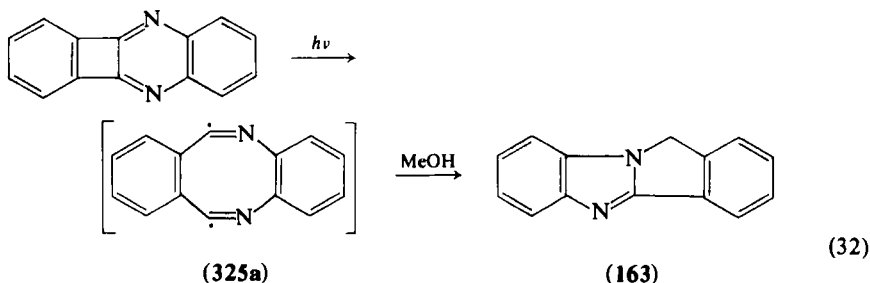
some examples of this type of transformation, in some cases involving prototropy as well as valence bond isomerization.



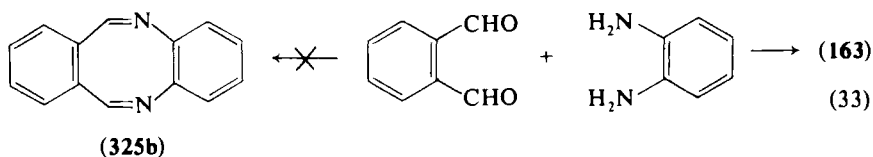
SCHEME 14

The transformation of cyclooctatetraene **315** to **316** has been achieved and is quoted^{387a} as an example of a $[\pi^4a + \pi^2a]$ cycloaddition, and the alternative transposition **317** \rightarrow **318** is also known.^{387b} For polyazacyclooctatetraenes (**319**, **321**, **323**, **324**), this type of cyclization can lead to heteroethylenic structures **320** or aromatic systems (**322**, **262**, **15**).

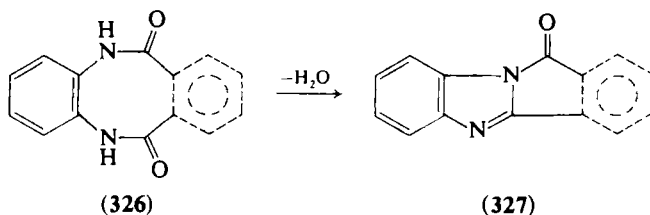
The ring closure **319** \rightarrow **320** has not been effected experimentally, though there are many reactions that could lead to 1,4-diazacyclooctatetraenes **319** where the product isolated is a pyrrolino[1,2-*a*]-imidazole **320** (this does not necessarily implicate **319** as an intermediate). Equations (32) and (33) are typical examples.



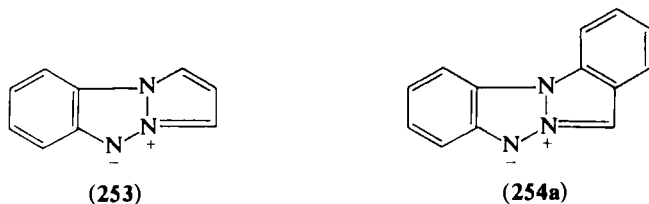
³⁸⁷ (a) T. L. Gilchrist and R. C. Storr, "Organic Reactions and Orbital Symmetry," p. 101. Cambridge Univ. Press, London and New York, 1972; (b) M. Jones and L. O. Schwab, *J. Am. Chem. Soc.* **90**, 6549 (1968).



The photoinduced isomerization in Eq. (32) is thought to involve a diradical intermediate **325a**.¹⁵⁷ The reaction of phenylenediamines with *o*-phthalic aldehydes [Eq. (33)] has been extensively explored^{315b, 321g, 323a} (also Section III,B,4,a), but in all cases **163** is formed. A transformation of type **319** \rightarrow **320** for which there is much information is the dehydration of diazocinediones **326** to imidazopyrrolones **327**, studied by Paudler and Zeiler^{315a} and others.^{315c, 321f, 324, 325}



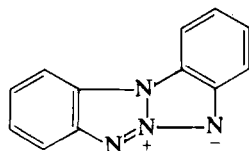
No examples of **321** \rightarrow **322** are known, though the aromatic character of **322** should favor such a transformation. Simmons *et al.*^{339, 388} have examined the related isomerization **324** \rightarrow **15** and concluded that the polyazapentalene forms **254b**, **255**, **328**, and **329** are stable. Related systems **253**,^{333a} **254a**,³³⁵ and **263**³⁵⁰ have been prepared, and in all cases the azapentalene structure has been unambiguously confirmed, in two cases (**255**³⁸⁹ and **263**^{351, 390}) by X-ray structures. Tetraazacyclo-octatetraenes **324** have not been detected and they are assumed to be transformed rapidly into azapentalenes.



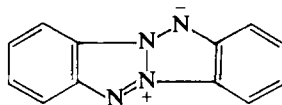
³⁸⁸ Y. T. Chia and H. E. Simmons, *J. Am. Chem. Soc.* **89**, 2638 (1967).

³⁸⁹ M. E. Burke, R. A. Sparks, and K. N. Trueblood, *Acta Crystallogr.* **16**, A64 (1963); B. M. Laing, R. A. Sparks, M. J. Laing, and K. N. Trueblood, *Acta Crystallogr.*, **B32**, 2518 (1976).

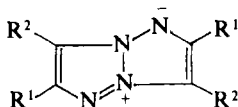
³⁹⁰ M. Brufani, W. Fedeli, G. Giacomello, and A. Vaciago, *Gazz. Chim. Ital.* **93**, 1556 (1963).



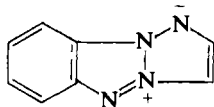
(254b)



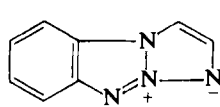
(255)



(263)

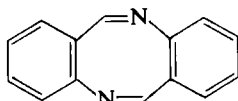


(328)

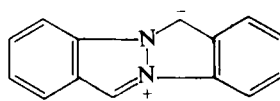


(329)

Paudler and Zeiler³⁹¹ prepared the diazadibenzocyclooctene **330** but were unable to effect its conversion into **331** (an example of **323** → **262**), either because **330** is the more stable, or because the activation energy separating **330** and **331** is too high. So dibenzo[*b,f*]-3a,6a-diazapentalene **331** remains unknown, although the parent 3a,6a-dibenzopentalene **262** has been synthesized, by a quite different route³⁴⁷ (Section III,C,1,b).



(330)



(331)

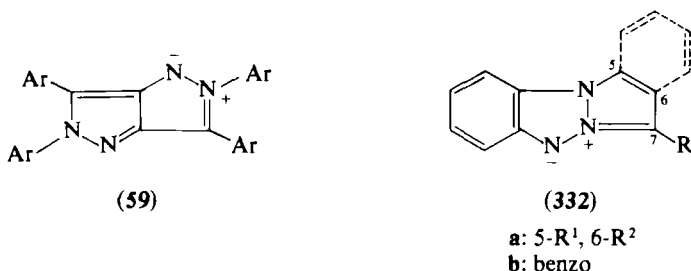
C. ELECTROPHILIC SUBSTITUTION

Like other π -excessive heterocycles⁹ (e.g., azoles), the main reactions of azapentalenes are electrophilic substitutions at electron-rich centers (nitrogen or carbon atoms) in the molecule.

1. Protonation

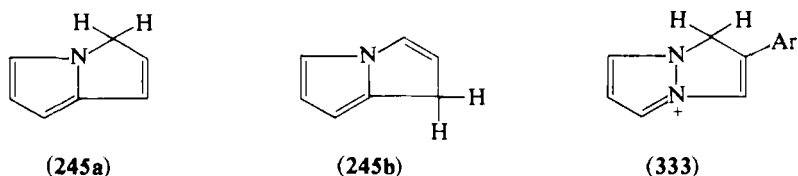
a. *C-Protonation*. Although mesoionic azapentalenes such as **59** and **332** formally carry a negative charge on a nitrogen atom, they are weak bases, more stable in the dipolar form than as the protonated monocation, despite the fact that the latter retains the 10- π -system. Two examples, one from type A compounds (**59**) and the other from type C (**332**) illustrate this behavior.

³⁹¹ W. W. Paudler and A. G. Zeiler, *Chem. Commun.*, 1077 (1967).



Compound **59** is weakly basic, insoluble in dilute mineral acids but soluble in concentrated sulfuric acid, from which it is precipitated on addition of water.^{115b} NMR has shown **332b** to undergo protonation at C-7 in trifluoroacetic acid, even though this destroys the aromaticity, rather than N-protonation.³⁹² Perchlorate salts of **332a** were isolated but their NMR spectra showed that C-7 protonation had not occurred.^{334b} N-Protonation may be involved in this case.

Katz³¹ has demonstrated that the 3a-azapentalene monoanion **246** (Section III,B,5) is readily protonated to give the weak conjugate acid **245a** ($pK_a = 29$), not the isomer **245b**. The conjugate acid **333** is also very weak, and a strong base (LiH/DMSO) is required to generate the 3a,6a-diazapentalene **262**.³⁴⁶



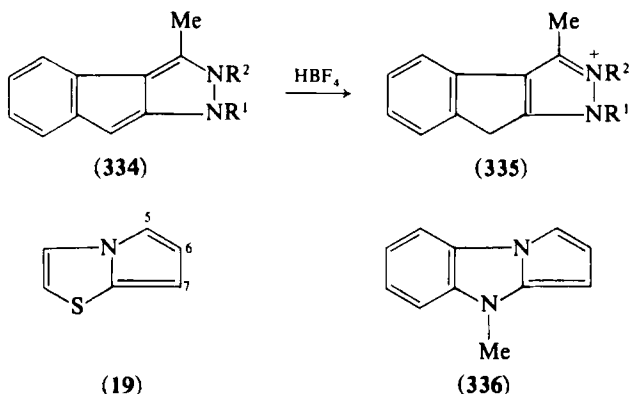
C-Protonation appears to be favored in azapentalenes lacking pyridinoid nitrogen atoms. In some cases (e.g., **334** → **335**),³⁵⁷ only one position can be protonated, in others (e.g., **19**,^{393–395} **336**²⁸¹), there is competition between carbon atoms. In these last two systems, protonation predominates at C-5, in accordance with electron-density calculations for **336**,²⁸¹ but C-7 protonation is also observed. NMR studies have demonstrated that some C-7 protonation occurs with the 5,6-dimethyl derivative of **19**,³⁹³ and that H/D exchange at C-7, though slower than at C-5, is still detectable.³⁹⁴

³⁹² O. Tsuge and H. Samura, *Chem. Lett.*, 175 (1973).

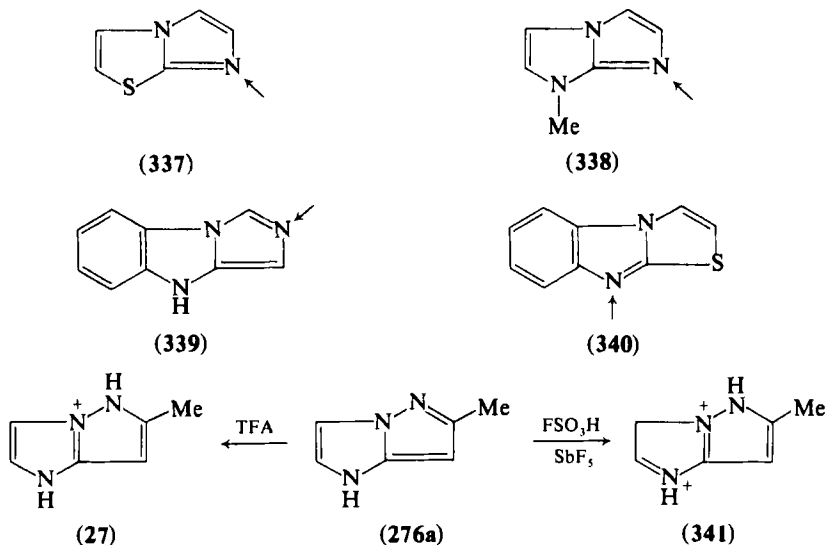
³⁹³ B. B. Molloy, D. H. Reid, and S. McKenzie, *J. Chem. Soc.*, 4368 (1965).

³⁹⁴ W. Engewald, M. Mühlstädt, and C. Weiss, *Tetrahedron* **27**, 4171 (1971).

³⁹⁵ R. K. Mackie, S. McKenzie, D. H. Reid, and R. G. Webster, *J. Chem. Soc., Perkin Trans. I*, 657 (1973).



b. *N*-Protonation. There are no systematic studies on the site of N-protonation in azapentalenes with several pyridinoid nitrogen atoms. Systems with one such nitrogen atom (e.g., **337**,^{254, 396, 397} **338**,^{210a} **339**,³⁹⁸ **340**,^{399a} and **276a**⁴⁰) all protonate in this position, and in the case



³⁹⁶ L. M. Alekseeva, G. G. Dvoryantseva, Yu. N. Sheinker, I. A. Mazur, B. V. Kurmaz, and P. M. Kochergin, *Khim. Geterotsikl. Soedin.* **10**, 1206 (1974).

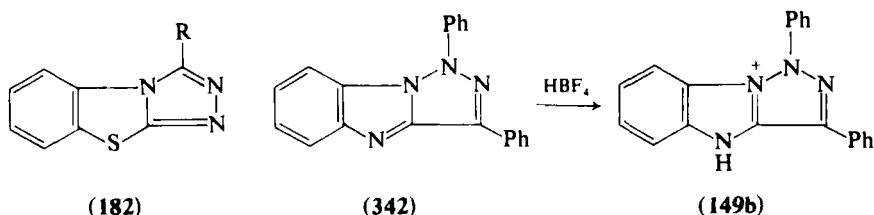
³⁹⁷ L. Pentimalli and G. Milani, *Ann. Chim.* **61**, 672 (1971).

³⁹⁸ G. G. Dvoryantseva, T. N. Ul'yanova, G. P. Syrova, Yu. N. Sheinker, V. M. Aryuzina, T. P. Sycheva, and M. N. Shchukina, *Teoret. Eksp. Khim.* **6**, 23 (1970).

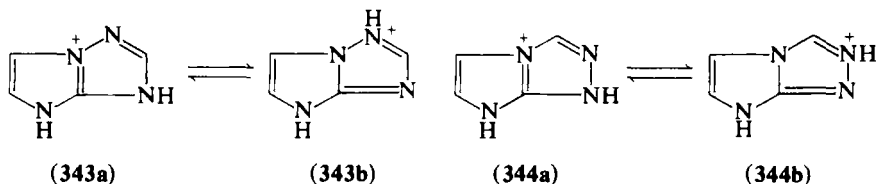
³⁹⁹ (a) G. G. Dvoryantseva, L. M. Alekseeva, T. N. Ul'yanova, Yu. N. Sheinker, P. M. Kochergin, and A. N. Krasovskii, *Khim. Geterotsikl. Soedin.* **7**, 937 (1971); (b) O. S. Anisimova, Yu. N. Sheinker, R. M. Palei, P. M. Kochergin, and V. S. Ponomar, *ibid.* **11**, 1124 (1975).

of **339**, the authors³⁹⁸ present a long argument to eliminate the pyrrole nitrogen or a ring carbon atom as sites of protonation. The imidazo-[1,2-*b*]pyrazole (**276a**) undergoes initial N-protonation to give **27**, and a second protonation on carbon to give **341**.⁴⁰

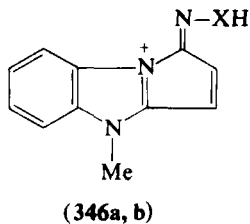
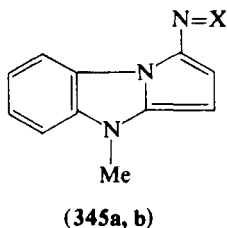
System **182**, with two pyridinoid nitrogen atoms, gives a perchlorate salt, but the structure has not been investigated.^{197b} The cation **149b** is claimed¹⁴⁹ as the product from **342**, though no structure proof is presented other than the presence of a broad NH^+ band at 2600 cm^{-1} in the IR spectrum. Structure **149b** seems likely since it relieves adjacent lone-pair interactions in **342** (see Section IV,A,1).



A study of the NMR spectra of imidazo[1,2-*b*]- and -[2,1-*c*]-*s*-triazoles in 98% sulfuric acid showed that structures bearing both protons on the *s*-triazole ring could be excluded, but the exact nature of the cations could not be determined.^{268b} CNDO/2 calculations on this system support structures **343a** and **344a**.^{268b}



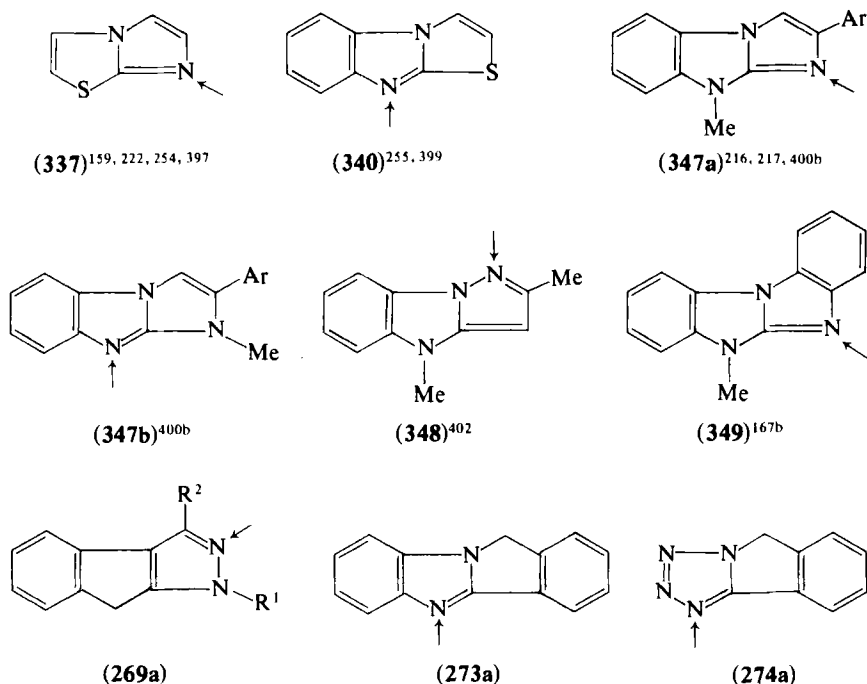
The phenylazo compound **345a** and the nitroso compound **345b**, both derivatives of **336**, protonate on the side chain, suggesting that the heteroatoms in these substituents are more basic than position 7 in the ring.^{285b}



a: X = NPh
b: X = O

2. N-Alkylation

Many quaternary salts have been prepared from systems possessing one pyridinoid nitrogen atom, and the position of alkylation in some examples is shown in Scheme 15. Usually iodomethane has been employed as the quaternizing agent, but reactions with phenacyl bromide²²² and N-aminations¹⁵⁹ are also known. In a few systems it has been possible to alkylate at an NH, then quaternize the same molecule with a dihalogeno-1,*n*-alkane, thus fixing a polymethylene chain between two nitrogen atoms.^{176b} Quaternization of CH tautomers (Section IV,A,1) followed by deprotonation has been used as a synthetic route to aromatic azapentalenes (Sections III,A,5; III,B,5), and quaternary salts of **269a**,^{121, 357} **273a**,^{322, 323d, 330} and **274a**³³² were prepared for this purpose. The site of quaternization of **274a** is the same as that of the monocyclic N-1-substituted tetrazole.⁴⁰¹



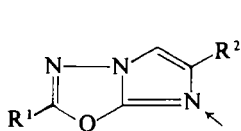
SCHEME 15

⁴⁰⁰ (a) V. A. Anisimova, A. M. Simonov, and T. A. Borisova, *Khim. Geterotsikl. Soedin.* **9**, 791 (1973); (b) V. A. Anisimova, A. M. Simonov, and A. F. Pozharskii *Khim. Geterotsikl. Soedin.* **9**, 797 (1973).

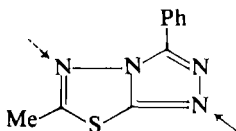
⁴⁰¹ D. M. Zimmerman and R. A. Olofson, *Tetrahedron Lett.*, 3453 (1970).

⁴⁰² J. Elguero and R. Lazaro, unpublished results.

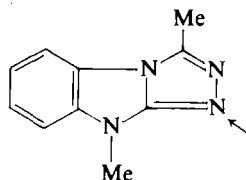
The site of quaternization in polybasic systems has been investigated in only a few systems: **208**,¹⁴⁶ **350**,¹⁴⁶ and **351**.⁴⁰³



(208)

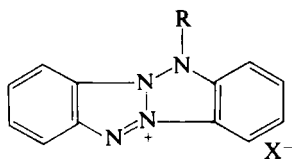


(350)

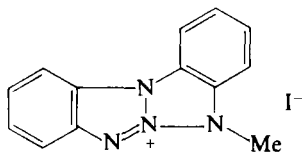


(351)

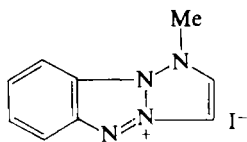
For mesoionic azapentalenes, N-substituted quaternary salts tend to be unstable, like their protonated counterparts (Section IV,C,1,a), and their preparation is sometimes difficult. Quaternary salts **352** can be prepared,³⁴⁰ but if the methiodide **352** (R = Me, X = I) is heated under reduced pressure the free base is recovered. Compound **353** is equally unstable,³³⁶ and **355** decomposes at 200° or on standing in any solvent other than iodomethane.³⁴⁰ The methylation product of **328** (probably **354** though the position of substitution is uncertain) is rather more stable,³⁴⁰ but a methiodide could not be isolated from **332a** (Section IV,C,1,a) even after prolonged heating with iodomethane.^{334b}



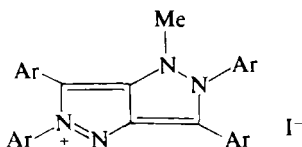
(352)



(353)



(354)



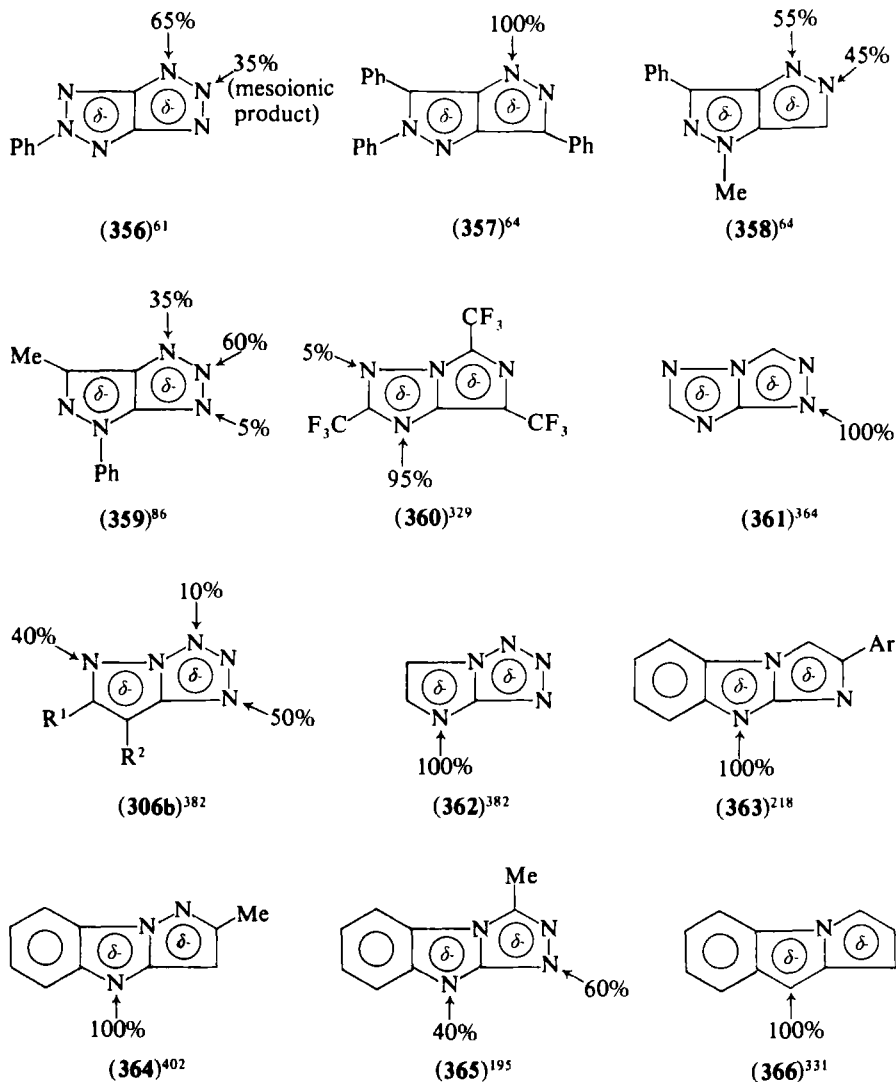
(355)

Alkylations of NH azapentalenes are carried out not on the neutral molecule, but on the corresponding anion. Methylations are usually performed with iodomethane or methyl sulfate on the silver salt,⁶¹ or, more frequently, on the sodium salt. Methylations with diazomethane may also be included since Gompper⁴⁰⁴ has shown that initial proton abstraction to give the methylating agent CH_3N_2^+ is involved. Scheme 16

⁴⁰³ J. de Mendoza and P. Rull, unpublished results.

⁴⁰⁴ R. Gompper, *Adv. Heterocycl. Chem.* 2, 245 (1963).

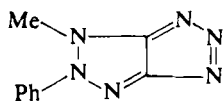
shows the relative proportions of alkylated products from a number of azapentalenes. Certain symmetrical systems, such as benzimidazo-[1,2-*a*]benzimidazole,^{167b} that can only give one product are not included.



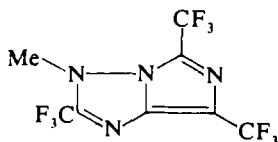
SCHEME 16

Examination of Scheme 16 reveals that the formation of alkylated products with two adjacent doublets is not favored, as illustrated by the absence of **367** from **356** and the low yield of **368** from **360**. These

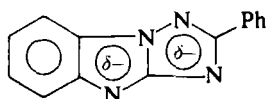
results suggest that the structure of the benzyl derivative of **369** is not likely to be **370**, as claimed in the literature²⁰³ without supporting evidence.



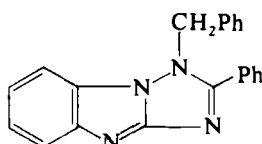
(367)



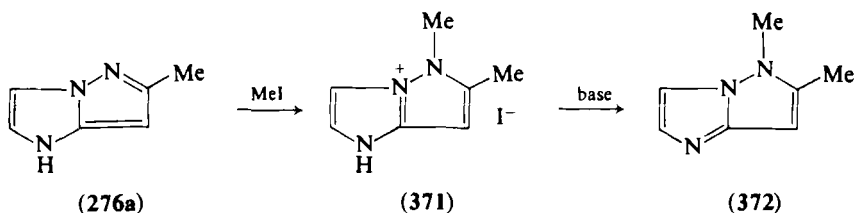
(368)



(369)



(370)



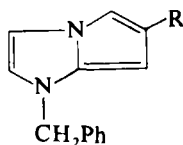
(276a)

(371)

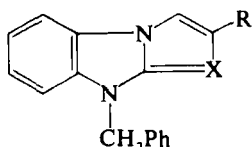
(372)

On treatment with neat iodomethane, **276a** gives the salt **371**, which is deprotonated to the base **372**.⁴⁰ It would seem that in this case the tautomeric structure controls the orientation of quaternization.

Removal of N-benzyl substituents from the compounds **373**,³⁸ **374a**,³⁸ **374b**,^{400a} and **375**²⁰⁵ was successfully achieved using sodium in liquid ammonia, but an attempt to debenzylate **376** by catalytic hydrogenation failed.¹⁷⁸

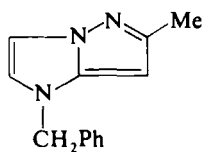


(373)

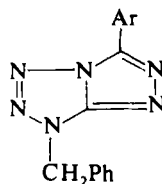


(374)

a: X = CH
b: X = N



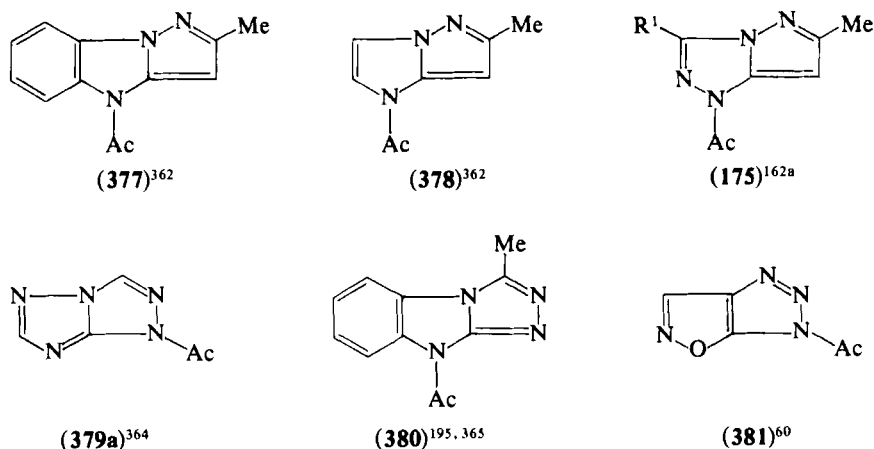
(375)



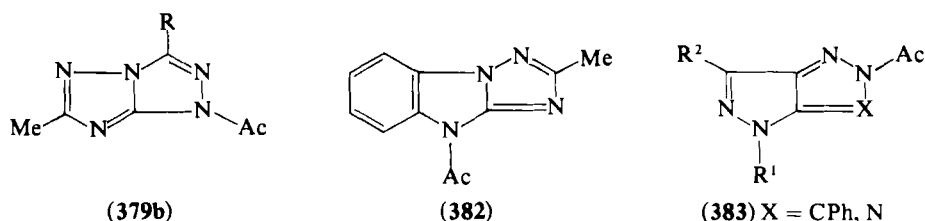
(376)

3. N-Acylation

The low activation energy of transacylation reactions means that the structure of N-acyl derivatives is thermodynamically controlled. Among monocyclic azoles it has been shown⁴⁰⁵ that, in the absence of steric effects, the structures of the most stable N-acyl derivatives parallel those of the most stable annular proton tautomers. The same results are seen in azapentalenes (Scheme 17), where the acyl derivatives **377**, **378**, **175**, **379a**, **380**, and **381** are structurally related to the stable tautomers **275b**, **276a**, **277a**, **278a**, **280a**, and **281a** (Section IV,A,1). A consideration of the "rules" proposed earlier (Section IV,A,1) to account for the stability of annular tautomers therefore allows structures **379b**^{202a, 202c} and **382**²⁰³ to be proposed for two compounds where the structures have not been determined.



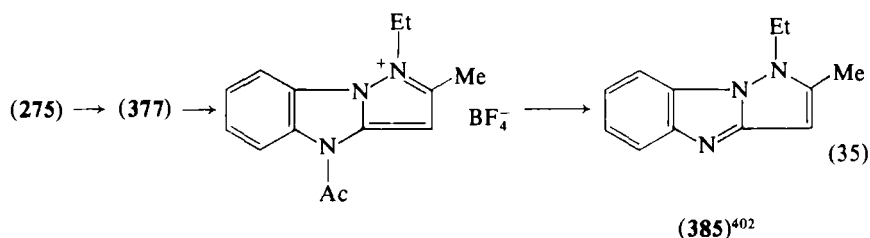
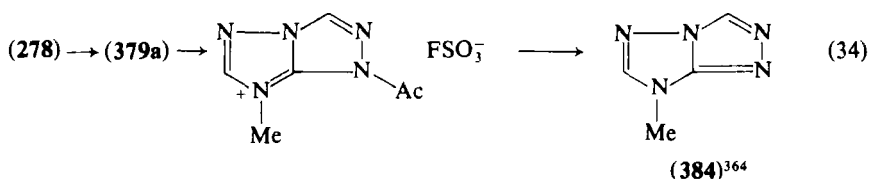
SCHEME 17



In pyrazolo[4,3-*c*]pyrazoles and pyrazolo[3,4-*d*]-*v*-triazoles, acyl derivatives of the type **383**, analogs of the stable NH tautomer (Section IV,A,1) are formed.^{65, 66b, 66c, 367}

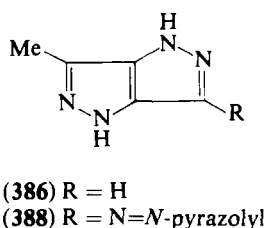
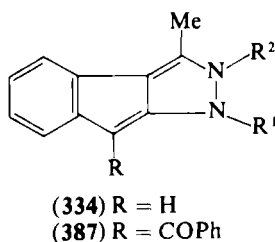
⁴⁰⁵ M. Begtrup, R. M. Claramunt, and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, in press.

N-Acyl derivatives of heterocycles can often be quaternized by "hard" alkylating agents, such as trialkyloxonium fluoroborates⁴⁰⁶ or methyl fluorosulfonate.³⁶⁴ The quaternary salt is not usually isolated, but *N*-alkylated derivatives are obtained whose structures are generally different from those obtained by alkylation of anions (Sections IV,C,2). This method, due to Olofson and Kendall,⁴⁰⁶ has been used with success in azapentalenes [Eqs. (34) and (35)], where the products **384** and **385** are different from those obtained by alkylation of the anions **361** and **364**, respectively (Scheme 16).



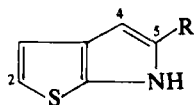
4. Electrophilic Substitution at Carbon

a. *Azapentalenes of Type A*. This class of compounds has been insufficiently studied to allow any general rules to be formulated, but a few examples will be discussed. Compound **334** undergoes substitution in the cyclopentadiene ring (treatment with benzoyl chloride gives **387**³⁵⁷), and **386** reacts with pyrazole diazonium salts to give the azo dye **388**.^{66c}



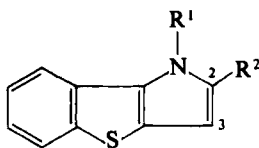
⁴⁰⁶ R. A. Olofson and R. V. Kendall, *J. Org. Chem.* **35**, 2246 (1970).

Most work, however, has been done on systems with several substitution sites. Formylation of the thieno[2,3-*b*]pyrroles (**389**) and (**390**) showed that in the former case, formylation takes place predominantly (90%) at C-5, and 10% at C-4. An electron-attracting substituent at C-5, as in **390**, orients substitution into the thiophene ring (95% at C-2).⁴⁰⁷



(**389**) R = H

(**390**) R = CO₂Et



(**391**) R¹ = R² = H

(**392**) R¹ = Me, R² = H

Shkurko and Mamaev^{50,408} have studied the 1*H*-benzothieno[3,2-*b*]pyrrole system **391** extensively. Electrophilic substitution (e.g., Mannich reaction, acetylation, diazonium coupling) takes place at C-2, as predicted by MO calculations.^{408b} If position 2 is occupied, substitution occurs at C-3.⁴⁴ The Vilsmeier reaction on the 2-aryl derivative gave the expected product, but bromination of the parent system **391** failed. A 3-bromo derivative was successfully obtained from the N-methyl compound **392** with bromine in chloroform.⁴⁴

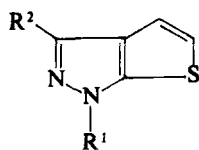
Snyder^{51a} has studied the 5-carbethoxy derivative of thieno[3,2-*b*]pyrrole (**460**, R = H) and shown that the Mannich reaction gives 6-substituted products and acetylation takes place at C-2. Bromination gave a 2,6-dibromo-compound, and the N-benzyl-derivative (**460**, R = CH₂Ph) yielded a 2-lithium-compound with butyllithium which was converted to a 2-carbomethoxy derivative.^{51b}

Recent work by Kvitko *et al.*⁴⁰⁹ on thieno[2,3-*c*]pyrazoles **393** has shown that bromination and formylation (Vilsmeier reaction) take place at C-2, i.e., α to sulfur, though benzothiophene generally substitutes in the β -position.^{409b} These Russian workers argue that, for **393**, a transition state such as **395** will be less unfavorable than the corresponding transition state **394** for benzothiophenes, since **394** has to adopt a quinonoid structure (see **90c** and **282b**, Section IV,A,1).

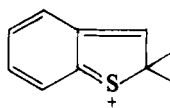
⁴⁰⁷ M. Farnier, S. Soth, and P. Fournari, *C.R. Hebd. Seances Acad. Sci., Ser. C* **277**, 1149 (1973); *Bull. Soc. Chim. Fr.*, 2511 (1975); *Can. J. Chem.* **54**, 1074 (1976).

⁴⁰⁸ (a) O. P. Shkurko and V. P. Mamaev, *Izv. Sibirsk. Otdel. Akad. Nauk SSSR Ser. Khim. Nauk*, 98 (1967) [*CA* **70**, 3876, 47330 (1969)]; (b) O. P. Shkurko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 184 (1968) [*CA* **69**, 26664 (1968)].

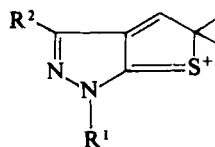
⁴⁰⁹ (a) I. Y. Kvitko and T. M. Galkina, *Zh. Org. Khim.* **5**, 1498 (1969); (b) Y. N. Koshelev, A. V. Reznichenko, L. S. Efros, and I. Y. Kvitko, *Zh. Org. Khim.* **9**, 2201 (1973).



(393)

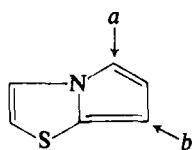


(394)

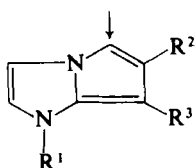


(395)

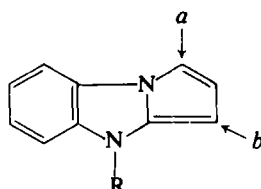
b. *Azapentalenes of Type B.* Since many different ring systems have been extensively studied, the results of a number of substitution reactions (except nitrations) are assembled in Scheme 18 and Table III. Scheme 18 shows the positions of substitution, and letters *a* and *b* indicate the preferential order of attack. Sometimes a mixture of products is obtained in which *a* predominates; more often, attack at *b* is only observed when *a* is substituted. Table III gives the reagents used and references.



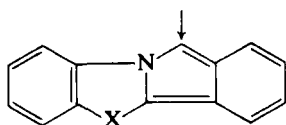
(396)



(397)

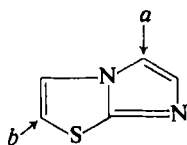


(398)

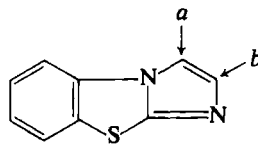


(399)

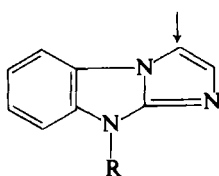
a: X = S
b: X = O



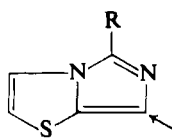
(400)



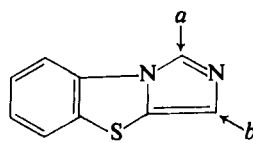
(401)



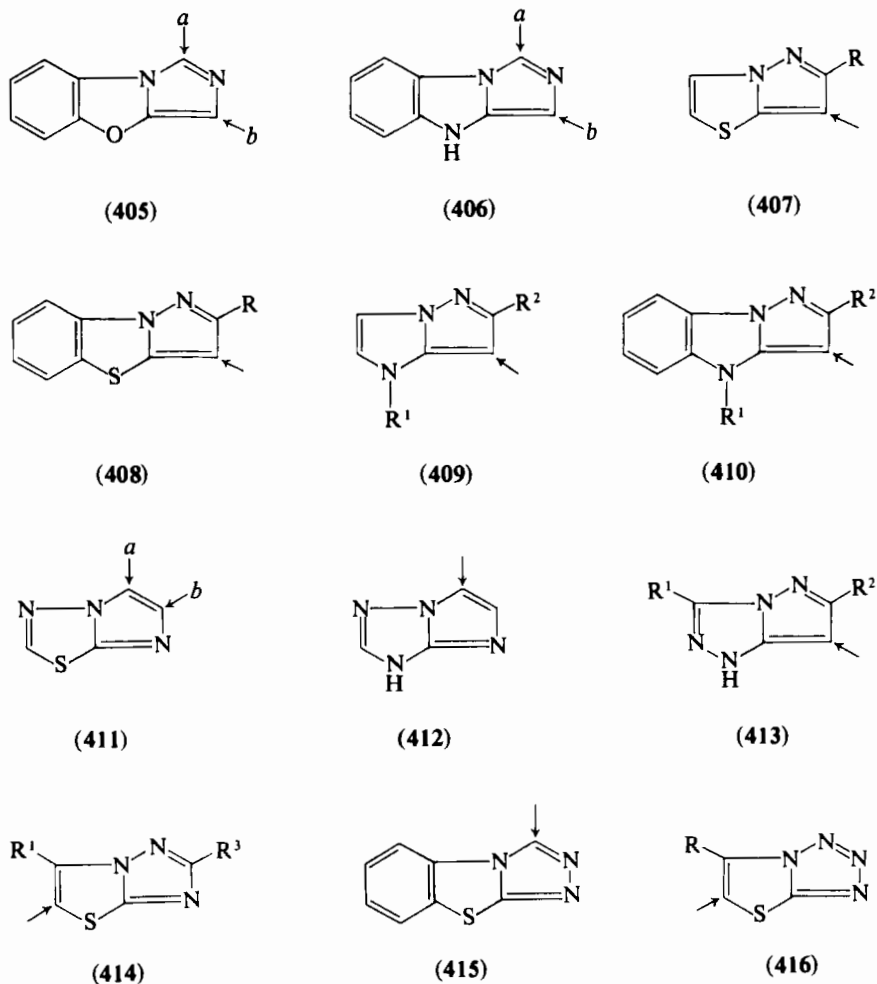
(402)



(403)



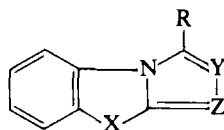
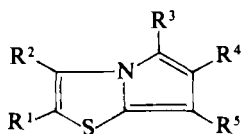
(404)



SCHEME 18

Certain groups of systems have been studied together; thus Pyl and Wünsch²⁷³ studied the reactivity of **396**, **400**, **403**, and **411** fairly extensively, and Sheinker *et al.*³⁹⁸ compared the reactivity of three closely related systems, **404**, **405**, and **406**, with the results of MO calculations. Reid *et al.*^{395, 410} studied pyrrolo[2,1-*b*]thiazoles (**396**), and in the course of this work prepared the first stable thioaldehydes, **425** and **426**, by treating the intermediate Vilsmeier salt with hydrogen sulfide.³⁹⁵

⁴¹⁰ S. McKenzie, B. B. Molloy, and D. H. Reid, *J. Chem. Soc. C*, 1908 (1966).

(425) $R^3 = \text{CHS}$ (426) $R^5 = \text{CHS}$ (427) $X = \text{NMe}$, $Y = \text{N}$, $Z = \text{CH}$, $R = (\text{CH}_2)_2\text{CN}$ (428) $X = \text{S}$, $Y = \text{CPh}$, $Z = \text{N}$, $R = \text{N}(\text{CO}_2\text{Et})\text{NHCO}_2\text{Et}$ (429) $X = \text{S}$, $Y = \text{CPh}$, $Z = \text{N}$, $R = \text{CH}(\text{CO}_2\text{H})\text{CH}_2\text{CO}_2\text{H}$

Bromination is usually performed with bromine in a suitable solvent, but in a few cases where this is ineffective (e.g., **415**^{197b} and **414**^{143b}), *N*-bromosuccinimide has been employed. In the case of **414**, bromination was found to be successful only when $R^1 = \text{Me}$. Chlorination of **410** has been achieved with sulfur chloride (Table III). Thiocyanations have been carried out either with bromine and ammonium thiocyanate^{307a} or bromine and thiourea^{236, 242, 414} though the structures of the products (thiocyanates or isothiocyanates) have not been established with certainty. Kano²⁴² showed that imidazo[2,1-*b*]-1,3,4-thiadiazole **411** undergoes bromination and thiocyanation preferentially at C-5 (position *a*, Scheme 18) when this position is free. C-5-substituted derivatives are brominated at C-6 (position *b*), but thiocyanation fails. Electrophilic substitution reactions in 1*H*-pyrrolo[1,2-*b*]-*s*-triazole have also been studied.^{289c}

Additions to compounds with activated double or triple bonds are known. Compound **406** ($R = \text{Me}$) gives **427** with acrylonitrile^{126d} (**405** does not react⁴¹⁸), and **401** reacts with diethyl azodicarboxylate and maleic anhydride to give **428** and **429**, respectively.^{416a} The 2,6-dimethyl derivative of **396** undergoes addition to dimethyl acetylenedicarboxylate at C-5 (position *a*, Scheme 18),⁴¹¹ but tetracyanoethylene gives both C-5 and C-7 (*a* and *b*) products, the latter predominating.⁴¹¹ Reid⁴¹⁰ had earlier reported that **396** reacts with bulky electrophiles to give mixtures of products and disubstituted derivatives.

Addition of **402** to the carbonyl group in formaldehyde can give the normal 3- CH_2OH derivative or a dimeric product **430**, according to the

⁴¹¹ O. Ceder and B. Beijer, *Tetrahedron* **28**, 4341 (1972).

⁴¹² F. S. Babichev and L. G. Khil'ko, *Ukr. Khim. Zh.* **40**, 946 (1974) [*CA* **82**, 16741 (1975)].

⁴¹³ (a) N. Saldabol, L. L. Zeligman, S. Hiller, J. Popelis, A. Abele, and L. N. Alekseeva, *Khim. Geterotsikl. Soedin.* **8**, 1353 (1972); (b) N. O. Saldabol, L. L. Zeligman, Y. Y. Popelis, and S. A. Hiller, *ibid.* **11**, 55 (1975).

⁴¹⁴ S. Kano, *Yakugaku Zasshi* **92**, 51 (1972) [*CA* **76**, 85728 (1972)].

⁴¹⁵ T. Pyl, K. H. Wünsch, and H. Beyer, *Justus Liebigs Ann. Chem.* **657**, 108 (1962).

⁴¹⁶ (a) L. Pentimalli and A. M. Guerra, *Gazz. Chim. Ital.* **97**, 1286 (1967); (b) L. Pentimalli and V. Passalacqua, *Boll. Sci. Fac. Chim. Ind. Bologna* **24**, 205 (1966).

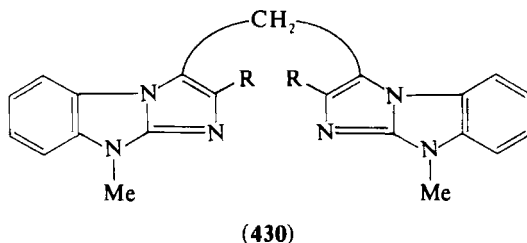
TABLE III
ELECTROPHILIC SUBSTITUTION REACTIONS: REFERENCES

	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416
278																					
Br					223a, 236, 413, 414	236	216, 417a		398	398 418	125, 127a, 416a			40	138a ^c 139e, ^c 139f ^c , 419 ^c	242	204b	129 ^d	143b	197b	307a
NO	29, 273, 411	276	285b	a: 28	223a, 226, 273, 413a, 415, 416a	416a	417b	128a 273			125 126d	205	205	205	139a						
NO ₂		276	285b		223b, 226, 273, - 415, 416a	416a	417a		398	398 418	127a, 416a					273	204b				307a
ArN ₂ diazo- coupling	29, 273	276	285b	a: 28	226, 273, 415, 416a, 416b	416a					127a, 127b				138b, 139f, 141d, 141f, 141h, 419			129a, 129b			

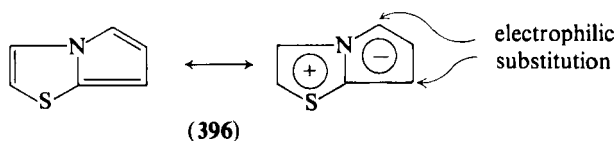
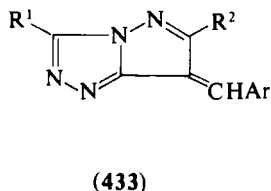
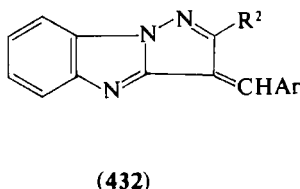
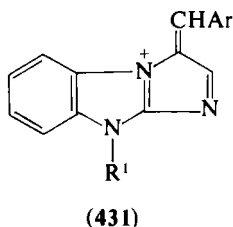
SCN				414	236				242		307a
CHO, Vilsmeier	29, 273 395 ^a 410	276	a: 28		217	398	398, 418	126d, 127b 416a			197b
COR	271 ^a 410	276	a: 28 b: 412	273		398	398 ^b 418 ^b	125 126d, 127b, 416a			
CH ₂ N(RR'), Mannich				208b	417c	398	398, 418	126d, 127a, 416a			197b
Condensation with >C=O	273	280, 285b	a: 28		417c	398	398 ^b 418 ^b	125 126d	138a, 138b, 139f, 402	129a, 129b	
Addition to double and triple bonds	411			226, 416a	416a 417c		418 ^b	126d, 416a			

^a CHS derivative.^b No reaction.^c Chlorination; sulfonation occurs at the same position. ^{138a}, ^{138b}, ^{139e}, ^{139f}^d Sulfonation also takes place at position 7. ^{129c}

conditions.^{417c} System **398** (Scheme 18) gives —CXNHCOPh ($\text{X} = \text{O}, \text{S}$) derivatives at position *a* on treatment with aroyl isocyanates or isothiocyanates.^{285a}



Many patents, especially from Agfa and Kodak, deal with the preparation of dyes for color photography by coupling with diazonium salts (Table III). Dyes have also been obtained by condensations with aromatic aldehydes; these may be salts (e.g., **431**)^{417c} or neutral molecules (**432**,⁴¹⁹ **433**^{129a}). Cyanine dyes containing a polymethine chain between the azapentalene ring and the aryl moiety are also known.^{129a, 417c, 419}



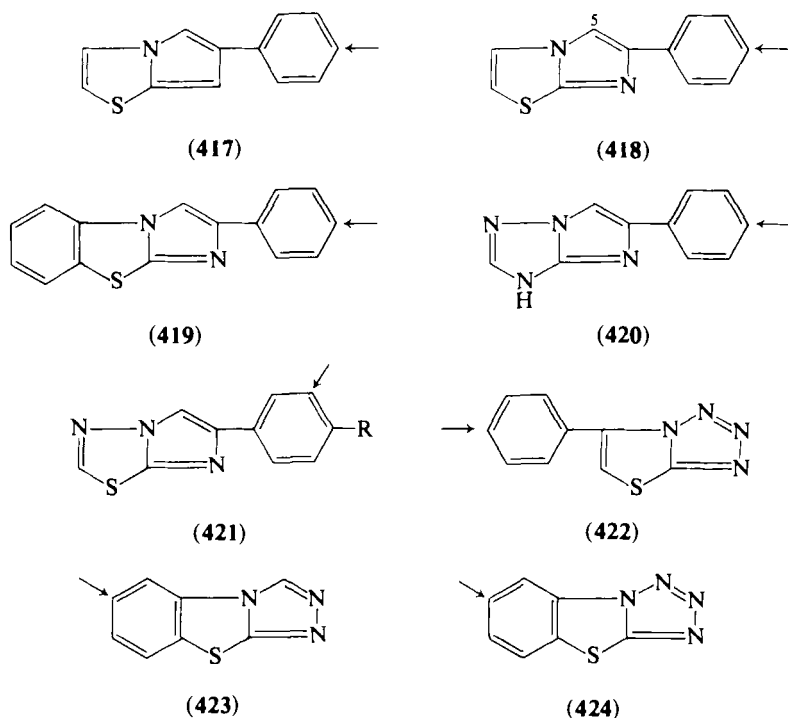
Scheme 18 shows that electrophilic substitution takes place in the ring which preferentially bears a negative charge (see Sections IV,A,1, V,B, and ref. 400b); **396** is a typical example.

⁴¹⁷ (a) V. A. Anisimova and A. M. Simonov, *Khim. Geterotsikl. Soedin.* **11**, 258 (1975); (b) A. M. Simonov, V. A. Anisimova, and N. K. Shub, *ibid.* **6**, 977 (1970); (c) A. M. Simonov and V. A. Anisimova, *ibid.* **5**, 669 (1969); (d) N. I. Avdyunina, V. A. Anisimova, and A. M. Simonov, *ibid.* **10**, 1577 (1974); (e) A. M. Simonov and V. A. Anisimova, *ibid.* **7**, 673 (1971).

⁴¹⁸ T. P. Sycheva, Z. A. Pankina, and M. N. Shchukina, *ibid.* **6**, 440 (1970); T. P. Sycheva, I. D. Kiseleva, and M. N. Shchukina, *ibid.* **6**, 444 (1970).

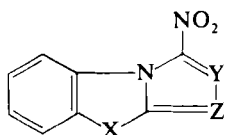
⁴¹⁹ K. H. Menzel, O. Wahl, and W. Pelz (Agfa A.-G.), British Patent 918,128 (1963).

c. *Nitration of Type B Azapentalenes.* Nitration was not discussed in the preceding section because the orientations of substitution in Scheme 18 are not always applicable. When the molecule contains a benzene ring, either *o*-condensed or as a substituent, nitration takes place either in this ring (Scheme 19) or in the azapentalene nucleus (Scheme 18), depending on the conditions.



SCHEME 19

Substitution in the azapentalene ring of **398** (Scheme 18) occurs with nitric/sulfuric acid to give compounds such as **434**.^{285b} In the same way, **402** gives **435** with potassium nitrate/sulfuric acid or by treating the nitrate salt of **402** with sulfuric acid,^{417a} and **436** results from the action of nitric/acetic acid on **404–406**.^{398, 418}

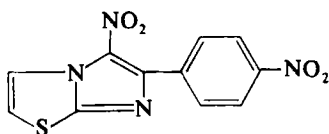


(434) X = NMe; Y = CR; Z = CH

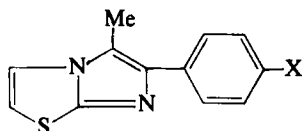
(435) X = NMe; Y = CR; Z = N

(436) X = S, O, NR; Y = N; Z = CPh

In cases where there is no free position on the azapentalene ring (e.g., **424**, Scheme 19) nitration occurs in the benzene ring.⁴²¹ For **417**²⁷³ and **423**^{197a} where both types of position are available, nitration occurs in the para position of the benzene ring (Scheme 19). Nitration in both positions is seen in imidazo[2,1-*b*]thiazoles.^{223b, 226, 415, 416a} The 6-phenyl derivative **418** gives a nitrate salt, which, on treatment with sulfuric acid is transformed into the *p*-nitrophenyl derivative.^{223b} Further nitration yields a dinitro compound **437**²²⁶ (cf. Scheme 18, attack at *a* on **400**), which can also be obtained directly from **418**.^{223b, 226} Nitration at C-5 occurs exclusively in **418** if the para position of the phenyl group is blocked,^{223b} and if C-5 is blocked as well, nitration takes place at C-2 (e.g., **438**^{223b, 415}) (cf. **400**, Scheme 18).

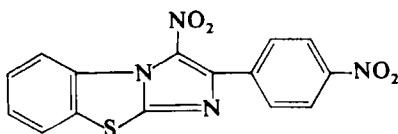


(437)

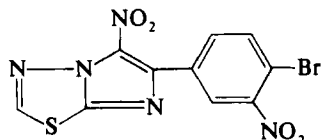


(438)

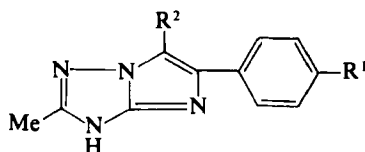
The corresponding 2-phenylimidazo[2,1-*b*]benzothiazole **419** (Scheme 19) is nitrated to give a mixture of the *p*-nitrophenyl derivative and the dinitro compound **439**.^{416a} The imidazo[2,1-*b*]-1,3,4-thiadiazole **421** (R = Br) (Scheme 19) gives a dinitro derivative **440**, and 2-methyl-5-phenylimidazo[1,2-*b*]-*s*-triazole gives two products according to the conditions. Nitric/sulfuric acid yields **441**, and **442** results from treatment of the nitrate salt of the base with sulfuric acid.^{204b}



(439)



(440)

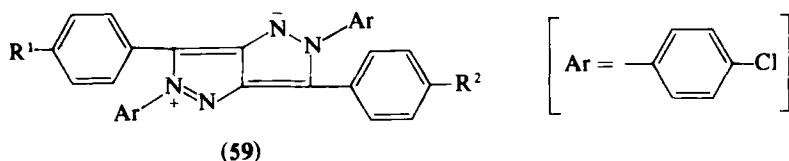
(441) R¹ = H; R² = NO₂(442) R¹ = NO₂; R² = H

⁴²⁰ (a) O. Tsuge and H. Samura, *Tetrahedron Lett.*, 597 (1973); (b) O. Tsuge and H. Samura, *Heterocycles* **2**, 27 (1974).

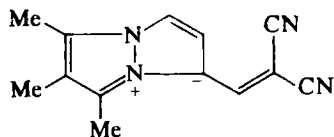
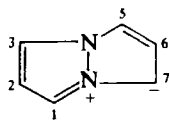
⁴²¹ V. N. Skopenko, L. F. Avramenko, V. Y. Pochinok, and M. I. Svichar, *Ukr. Khim. Zh.* **39**, 215 (1973) [*CA* **78**, 147878 (1973)].

The fused tetrazole **422** (Scheme 19) was originally assumed^{307a} to be nitrated on the thiazole ring, but recent NMR studies have shown that a *p*-nitrophenyl derivative is formed.^{185b} Since **422** (and **424**) display azide \rightleftharpoons tetrazole tautomerism (Section IV,B,1), the exact structure of the reacting species is unknown, but the product exists predominantly as the azide.

d. *Mesoionic Azapentalenes*. Compound **59a** is one of the few type A mesoionic systems that has been studied. Nitration leads to **59b**, whereas bromination gives both mono- (**59c**) and dibrominated derivatives (**59d**).^{115b}



- a: $R^1 = R^2 = H$
 b: $R^1 = R^2 = NO_2$
 c: $R^1 = Br; R^2 = H$
 d: $R^1 = R^2 = Br$

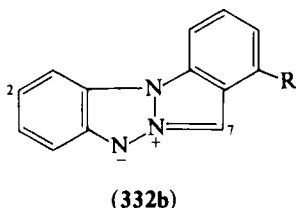
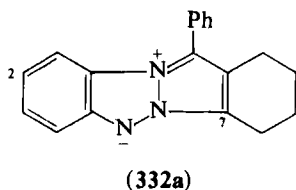


Potts and McKeough⁸¹ have shown that thieno[3,4-*c*]pyrroles (**84**) and thieno[3,4-*c*]pyrazoles (**83**) undergo 1,3-dipolar cycloadditions with certain dipolarophiles. Adducts from **84** in some cases eliminated hydrogen sulfide to give isoindoles.

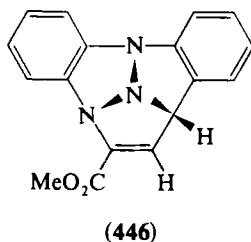
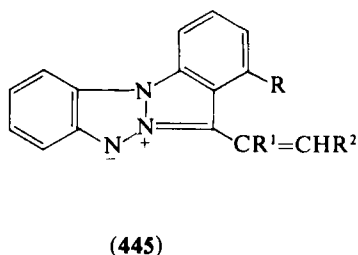
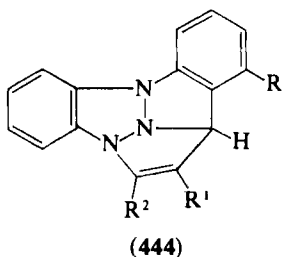
Most mesoionic azapentalenes have two nitrogen atoms at the ring junctions (type C), and their reactivity has been fairly well explored. Derivatives of 4,8-diazapentalene **262** have been studied by Solomons and Voight,³⁴⁵ and by Trofimenko.^{344, 347} Although initial attempts at substitution reactions failed,³⁴⁵ derivatives have since been prepared in this way.^{344, 347}

The parent system reacts with acetic anhydride, benzoyl chloride, and cyanogen chloride to give the 5,7-diacetyl-, -dibenzoyl-, and -dicyano derivatives, respectively. The 2-bromo derivative of **262** undergoes 1,3-disubstitution with these reagents, and the 1,2,3-trimethyl derivative reacts with ethoxymethylenemalononitrile to give the monosubstituted derivative **443**.

Tsuge and Samura^{335, 392, 420} have closely examined the reactivity of the triazapentalene **332b**. The Vilsmeier reaction and acetylation lead to 7-derivatives, and nitration, even in 10% aqueous nitric acid, gives a 2,7-dinitro derivative, though the position of the 2-nitro group was only tentatively assigned.³⁹² Bromination of a closely related compound (**332a**) in which the 7-position is blocked, occurred at C-2, but nitration gave an unidentifiable mixture.^{334b}

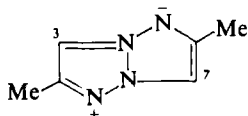


Compounds **332a, b** possess an azomethine imine structure and should undergo cycloaddition reactions.^{420a} Although dimerization of **332b** has not been observed,³³⁵ dipolarophiles yield cycloadducts **444** and "Michael adducts" **445**.^{420a} The structure of the product obtained from methyl propiolate, an unsymmetrical acetylene, has been studied by NMR and shown to be **446**.^{420b}



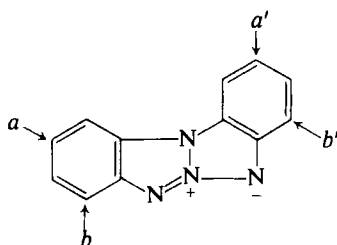
Among tetraazapentalenes, early work by Pflieger *et al.*³⁵⁰ on 2,6-dimethyl-*v*-triazolo[2,1-*a*]-*v*-triazole **447** showed that mono- and di-substituted products were formed. Bromination, nitration, and benzylation lead to 3,7-disubstitution, whereas 3-monosubstitution resulted from nitrosation, acetylation, carbethoxylation, and diazotization. Iodin-

ation and the Vilsmeier reaction lead to mixtures of both products, and chlorination results in substitution of the methyl groups in addition to 2,6-disubstitution.

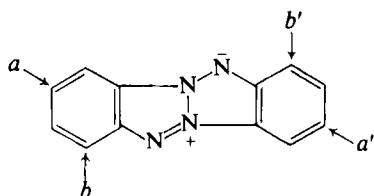


(447)

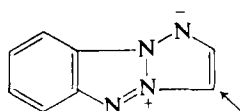
More recently, a research group at the DuPont de Nemours Company has studied the benzo derivatives **254b**, **255**, **328**, and **329**.^{336, 340, 388} Scheme 20 shows the preferred substitution positions in these compounds; experimental results are generally in accord with ground-state electron density calculations³⁸⁸ (Section V,B). Compounds **255**³⁴⁰ and **254b**³³⁶ have been particularly closely studied.



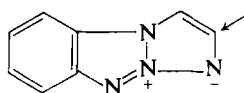
(254b)



(255)



(328)



(329)

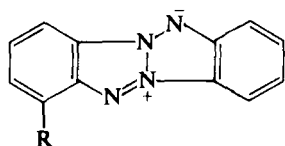
SCHEME 20

Monosubstitution at *a* occurs in **255** with *N*-bromosuccinimide, *N*-chlorosuccinimide, and 25% nitric acid at 0°; disubstitution (*a a'*) occurs with bromine or chlorine in acetic acid, thionyl chloride, chlorosulfonic acid, and 70% nitric acid; and tetrasubstitution (*a a' b b'*) is obtained with 90% nitric acid; **254b** behaves similarly. Tetracyanoethylene forms π -complexes with **255** and **328**,³⁴⁰ and the latter compound is slowly converted on standing to a C-substituted derivative with loss of HCN.

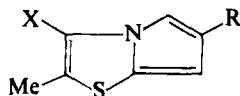
D. REACTIONS OF SUBSTITUENTS

1. Nucleophilic Substitution

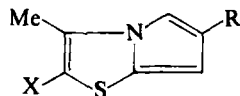
In common with other aromatic systems, halogen can be displaced from azapentalenes by nucleophiles. Examples include displacement of Br by NR_2 ^{168, 216} or NO_2 ^{216, 417a} in derivatives of **402**, by CN in derivatives of **404**,^{128d} by OR in derivatives of **405**,⁴¹⁸ and by OAr in **413**.^{129c} Conversion of Br to CO_2H via the Grignard reagent is known for derivatives of **393** ($\text{R}^3 = \text{Br}$),^{409b} and hydrogenolysis of chlorine with hydriodic acid and red phosphorus has been reported²³⁴ for a derivative of **404**. Few other nucleophilic displacements are known. The methyl derivative **448** was obtained from **255** with butyllithium and iodomethane,³⁴⁰ and various compounds **449** and **450** ($\text{X} = \text{D}$, CHO, CO_2^-) were also prepared from the appropriate lithio derivatives.⁴¹¹



(**448**) $\text{R} = \text{Me}$
 (**255**) $\text{R} = \text{H}$



(**449**)



(**450**)

As expected, nucleophilic substitutions in **449** and **450** take place in the more "basic" ring (cf. **396**, Section IV,C,4,b). These results are in accordance with CNDO/2 calculations (Section V,B).

2. Miscellaneous Reactions

Table IV shows some miscellaneous reactions of substituents on various ring systems. In many cases these reactions have been used to remove a substituent and thus prepare the parent ring system.

Certain acetyl and benzoyl derivatives are surprisingly hydrolyzed in acidic media to the corresponding acid and the unsubstituted azapentalene (Table IV). This phenomenon appears to occur in "compounds with an acyl group on a carbon atom where there is enhanced electron density."²⁸⁰

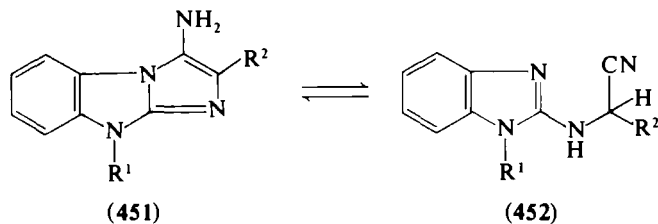
TABLE IV
 MISCELLANEOUS REACTIONS OF SUBSTITUENTS

Reaction	Parent ring system and references ^a
COOH → H	413, ^{161a} 393, ⁹² 400, ^{248a} 397, ³² 39, ^{422a} 390 ³⁷²
CHO → CH=NR	404, ^{128d} 405, ⁴¹⁸ 406, ^{127b} 402, ²¹⁷ 415 ^{197b}
CHO → COOH	393 (R=CHO) ^{409b}
CO → CH ₂	396, ^{271a} 397 ³²
COCH ₃ → C≡CH	402 ^{417d}
CH ₂ NR ₃ → CH ₂ CN	Thieno[3,2- <i>b</i>]pyrrole ^{422b}
NO ₂ → NH ₂	400, ²²⁶ 402 ^{417e}
NO → NH ₂	400, ²²⁶ 402, ^{417e} 410 ^{139a}
NH ₂ → NHNH ₂	396 ^{223c}
NH ₂ → NHCOR	390, ^{72b} 410 ^{141e}
NH ₂ → N ₂ ⁺	390 ^{72b}
NH ₂ → OH	396 ^{271b}
NH ₂ → H	180 ^{199, 200}
SH → H	404, ^{128c} 180 ^{199, 200}
COR → H	333, ^{343, 346} 397, ³² 398, ²⁸⁰ 399a, ²⁸ 400 ^{29, 30}
(R=Me, Ph)	407, ²⁰⁵ 409 ²⁰⁵

^a Systems 396–416 are illustrated in Scheme 18, Section IV,C,4,b.

E. RING CLEAVAGE REACTIONS

Except in one case, 451–452,^{417e} where an equilibrium is involved, reactions of this type are irreversible. Table V shows conditions under which one of the five-membered rings is cleaved in various azapentalenes.



Unsymmetrical systems can in principle undergo cleavage in either ring. Table V shows that benzazoles are more stable than azoles (e.g., in 415, 348, and 405) and that the *s*-triazole ring is more stable than the oxadiazole or thiadiazole ring (e.g., in 299c, 303, and 183).

⁴²² (a) R. L. Keener, F. S. Skelton, and H. R. Snyder, *J. Org. Chem.* **33**, 1355 (1968);
 (b) A. J. Humphries, R. L. Keener, K. Yano, F. S. Skelton, E. Freiter, and H. R. Snyder, *ibid.* **37**, 3626 (1972).

TABLE V
 RING CLEAVAGE OF AZAPENTALENES

Conditions	Ring system (Section)	Ring that is cleaved	References
Basic: OH ⁻	415 (IV,C,4,b)	s-Triazole	197b
	348 (IV,C,2)	Imidazole	216
	N ₂ H ₄ 299c (IV,A,2,b)	1,3,4-Thiadiazole	423
	OH ⁻ 303 (IV,A,2,c)	1,3,4-Thiadiazole	202c
Acidic: HOAc	183 (III,B,1,g)	1,3,4-Oxadiazole	182
Oxidative: KMnO ₄	405 (IV,C,4,b)	Imidazole	418
	KMnO ₄ 447 (IV,C,4,d)	(Symmetrical)	350
	KMnO ₄ 59 (IV,C,1,a)	(Symmetrical)	115b
	Chloramine 45 (III,A,1,b)	(Symmetrical)	5
	Peracid 255 (IV,C,4,d)	(Symmetrical)	339
Reductive: LiAlH ₄	255 (IV,C,4,d)	(Symmetrical)	339
	H ₂ /PtO ₂ 59 (IV,C,1,a)	(Symmetrical)	115b

F. OXIDATION-REDUCTION REACTIONS

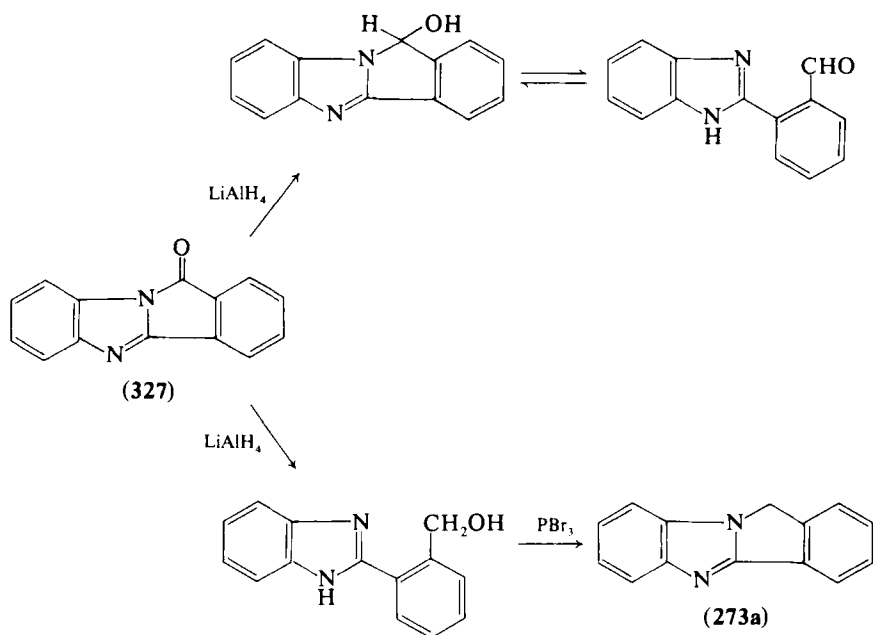
Transposition reactions of diazocinediones (Sections III,B,4,a and IV,B,2) can lead to compounds that are aza or benzo derivatives of two basic systems: **453** and **454**.^{165, 314, 321, 323, 331, 424} Two groups of workers^{323c, 323d} examined the reduction of **327** with lithium aluminum hydride, and the results of the earlier, more complete study^{323c} are shown in Scheme 21.



Attempts to reduce 8- π azapentalenes to 10- π systems have not been successful; thus **455** failed to give **80a** with Li/NH₃ or NaBH₄.^{3e} The reverse process (oxidation of a 10- π system) has also been attempted, but oxidation of indolo[3,2-*b*]indole **45** with chloramine⁵ did not give **456**; instead, ring cleavage occurred (Section IV,E; Table V).

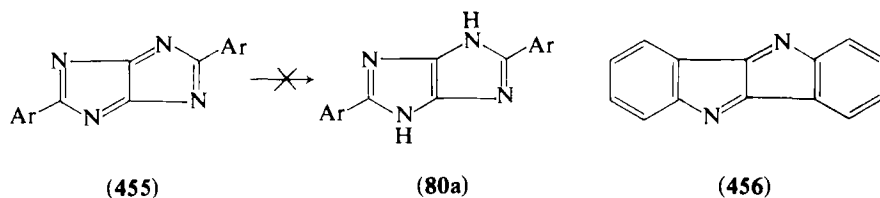
⁴²³ I. Y. Postovsky, A. D. Sinegibskaya, and E. G. Kovalek, *Khim. Geterotsikl. Soedin.* **11**, 566 (1975).

⁴²⁴ Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **21**, 1658 (1973).



SCHEME 21

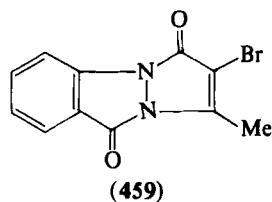
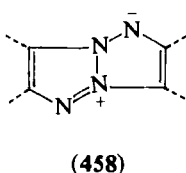
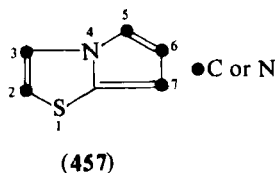
Certain quaternary salts of type B azapentalenes have been reduced to dihydro derivatives,^{167b} but reduction of neutral systems has been generally less successful.^{212, 355}



V. Physicochemical Properties

A. CRYSTAL STRUCTURES

The crystal structure determinations in the literature largely concern compounds of type B with a sulfur atom at position 1 (457), or tetraazapentalenes of type C (458).



Systems of type **457** which have been examined include 6-phenyl-imidazo[2,1-*b*]thiazole **417**,^{130b} 2-methyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole **350**,^{425a} three 5-thioformyl derivatives of pyrrolo[2,1-*b*]thiazole **425**,⁴²⁶⁻⁴²⁸ and tetrazolo[1,5-*b*]benzothiazole **312b**.³⁸⁵ All these molecules were found to be planar or near planar (dihedral angles between the two five-membered rings $< 5^\circ$) with C—S—C angles $\sim 90^\circ$. The E/Z configuration of the thioformyl group in the three derivatives of **425** was found to depend on the size of the 3- and 6-substituents.⁴²⁶⁻⁴²⁸ Interatomic distances measured for tetrazolo[1,5-*b*]benzothiazole **312b** led to the conclusion that there was no conjugation between the benzene ring and the tetrazole ring³⁸⁵ (see Section VII). An azapentalene related to **457** having only nitrogen atoms has been recently studied^{425b}; the pyrazolo[1,5-*d*]tetrazole **308** ($R^1 = \text{Me}$, $R^2 = \text{CO}_2\text{Et}$).

Among systems of general formula **458**, dibenzotetraazapentalene **255**³⁸⁹ and two derivatives of tetraazapentalene **263**^{351, 390} have been shown to be planar, along with a related system in a higher oxidation state, **459**⁴²⁹ (Section IV,F).

The crystal structure of a type A azapentalene, a substituted derivative of pyrazolo[3,4-*d*]thiazole **284**, has been reported,³⁷⁰ but it would be desirable to have information on unsubstituted type A systems, as well as on derivatives of type B lacking sulfur.

B. QUANTUM MECHANICAL CALCULATIONS

Generally speaking, little work has been reported on type A compounds, type B systems are being increasingly studied, and type C azapentalenes received a good deal of attention during the period 1966–1968.

⁴²⁵ (a) J. M. Forníes-Marquina, C. Courseille, and J. Elguero, *Cryst. Struct. Commun.* **3**, 7 (1974); (b) E. Alcalde, R. M. Claramunt, J. Elguero, and C. P. Huber, *J. Heterocycl. Chem.*, in press.

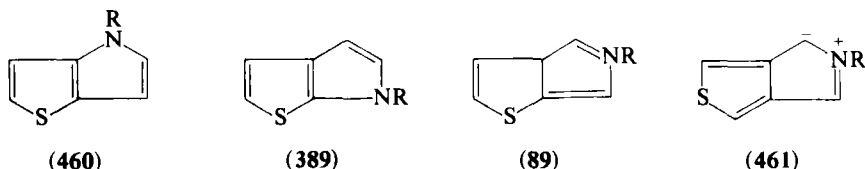
⁴²⁶ A. Sharma and R. C. G. Killeen, *Acta Crystallogr., Ser. B* **30**, 2869 (1974).

⁴²⁷ R. C. G. Killeen, J. L. Lawrence, J. U. Cameron, and A. Sharma, *Acta Crystallogr., Ser. B* **31**, 1217 (1975).

⁴²⁸ A. Sharma, J. L. Lawrence, and R. C. G. Killeen, to be published; A. Sharma, Ph.D. Thesis, University of St. Andrews (1973).

⁴²⁹ I. Sætøfte, *Acta Chem. Scand.* **27**, 661 (1973).

Trinajstić *et al.*⁴³⁰ examined some type A systems containing sulfur, including various thienopyrroles: **460** (R = H), **389** (R = H), **89** (R = H), and **461** (R = H). Dewar's method was used for ground-state calculations and the method of Pariser and Parr for the excited state, though sulfur *d*-orbital contributions were ignored. Calculated electronic transitions corresponded to those found from UV spectra (Section V,E) for **460** (R = H),^{431a} **389** (R = CH₂Ph),^{431b} and **89** (R = Et),^{84a} and a relative order of stability (**460** ~ **389** > **89** >> **461**) was determined based on calculated values for heats of atomization, aromatic stabilities, and ionization potentials. The same stability order is found using a graphical method that does not involve calculations.¹⁵ Compound **461** is predicted to exist as a triplet in the ground state. The correlation between stability and vertical ionization potential is worth noting as other examples will be seen later.



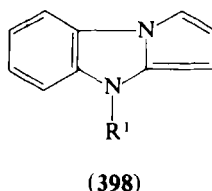
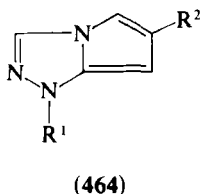
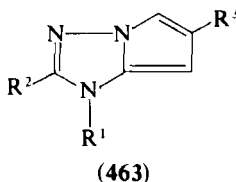
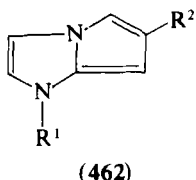
Much work has been reported on type B azapentalenes, and this can be classified according to the degree of sophistication of the calculations. Simple Hückel linear combination of atomic orbitals (LCAO) methods have been widely used, though more recently more sophisticated Pariser–Parr–Pople (PPP) methods (using only π -electrons) and “all-electron” CNDO calculations have been reported.

Okamura and Katz^{31a} studied the 3a-azapentalene anion **246** by the Hückel method and compared calculated π -charges with those obtained from proton chemical shifts after correction for the effect of the adjacent ring. They also attempted to correlate basicity with the difference in delocalization energies between the anion and the neutral molecule “with a limited degree of success.”²⁰ Boekelheide and Fedoruk³² compared calculations on the pentalene dianion **2** and 3a,6a-diazapentalene **262a** with those on pyrrolo[1,2-*a*]imidazole **462** (R¹ = R² = H) and concluded that electron-attracting groups and pyridinoid nitrogen atoms should stabilize these systems. Electron-density calculations by Babichev *et al.*²⁸¹ on pyrrolo[1,2-*a*]benzimidazole **336** are in agreement with experimental reactivity (Sections IV,C,1,a and IV,C,4,b) and more recently

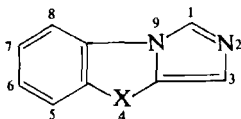
⁴³⁰ L. Klasinc and N. Trinajstić, *Tetrahedron* **27**, 4045 (1971).

⁴³¹ (a) D. S. Matteson and H. R. Snyder, *J. Org. Chem.* **22**, 1500 (1957); (b) R. K. Olsen and H. R. Snyder, *ibid.* **30**, 184 (1965); (c) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 1597 (1960).

the same Russian group has studied the four systems **462**, **463**, **464**, and **398** in the same way.⁴³²



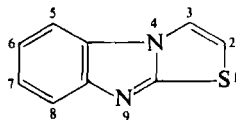
Sheinker *et al.*^{398, 399a} have studied systems **404**, **405**, **406**, and **340**. Calculations on the first three systems showed that their π -electron delocalization energies (DE)²⁰ are of the order of 0.37β , which is close to the values of condensed hydrocarbons. Free-valence indices indicate that imidazo[1,5-*a*]benzimidazole **406** is the least stable. Reactivity toward electrophiles at positions 1 and 3, protonation at position 2, and chemical shift data (Section V,G,2) are consistent with calculated electron densities.³⁹⁸



(404) X = S

(405) X = O

(406) X = NH



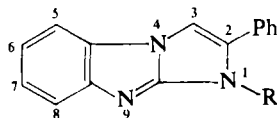
(340)

For **340** and the corresponding cation, π -electron densities relative to benzene were successfully compared with those deduced from chemical-shift data (Section V,G,2) after correction for the effects of ring current, anisotropy of lone pairs, and the electric field of the π -electrons.^{399a}

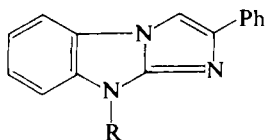
Simonov *et al.*^{400b} compared the reactivities of isomers **465** and **466** and found that the electron density at position 3 is greater for tautomer

⁴³² L. I. Savranskii, V. A. Kovtunencko, and F. S. Babichev, *Khim. Geterotsikl. Soedin.* **10**, 261 (1974).

466 ($R = H$), which is in accord with an "azulene-type" structure for this system (Section VII). In practice it is found that bromination of **465** at C-3 is difficult, whereas hydroxymethylation takes place on the benzene ring (compare with the behavior of **402**, Scheme 18, Section IV,C,4,b).



(465)



(466)

A simple Hückel (HMO) calculation by Kovalev *et al.*³⁷⁷ on system **299** (Section IV,A,2,b) predicted that the thione tautomer **299c** should be most stable, and this is in fact observed.

More sophisticated calculations using only π -electrons, notably of the PPP type, have been used in some cases,^{230, 394, 433} in particular to correlate the rate of exchange of protons on positions 1 and 3 in 2-methylpyrrolo[2,1-*b*]thiazole (Section IV,C,1,a) with localization energies.³⁹⁴

Among "all electron" methods, that of CNDO in its variants CNDO/2 and CNDO/S has been most used. Particularly worthy of note is the work of Galasso⁴³⁴ where π -electron methods are compared with "all valence electron" methods for the 3a-azapentalene anion **246** and 3a,6a-diazapentalene **262a**. The conclusion drawn from this study was that σ -core polarization plays a fundamental role in determining overall charge distribution in the ground state but is relatively less important in interpreting electronic spectra.

The work of Taddei *et al.*²³⁰ on imidazo[2,1-*b*]thiazole **337** and derivatives has interesting implications on the structure of azapentalenes, and an important aspect of this study is that the molecular geometry used for calculations on 6-phenylimidazo[2,1-*b*]thiazole **417** was obtained from X-ray structure determinations^{130b} (Section V,A). The reactivity of this system (Scheme 18, Section IV,C,4,b) is better correlated with π -electron densities than with total charges, and π -bond orders (by the PPP method) show that the thiazole part of the molecule is more localized than the imidazole part (Section VII). Proton chemical shifts, except that of the H_2 proton α to sulfur (Section V,G,2), vary linearly with the total charge carried by the ring carbon atoms.

Other CNDO calculations on type B azapentalenes have been carried

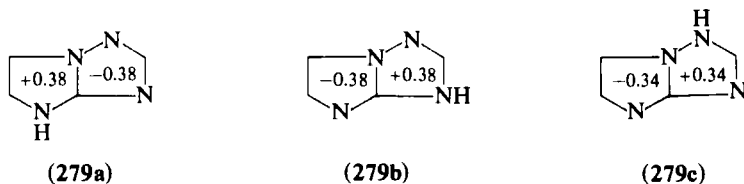
⁴³³ R. Faure, E. J. Vincent, and J. Elguero, *Tetrahedron Lett.*, 2703 (1973).

⁴³⁴ V. Galasso, *Gazz. Chim. Ital.* **99**, 1078 (1969).

out by the same authors,^{268b, 360, 433, 435-437} and many different molecular properties have been calculated: the relative stabilities of tautomers (Section IV,A,1) taking account of solvation energies, electronic spectra (Section V,E), ionization potentials, dipole moments, charge densities, and bond indices. Calculations relating solely to dipole moments are discussed later (Section V,C). The following systems have been studied: 6-methylimidazo[1,2-*b*]pyrazole **276**,^{360, 433} pyrazolo[3,2-*c*]-*s*-triazole **277**,^{268b, 360} *s*-triazolo[4,3-*b*]-*s*-triazole **278**,⁴³³ imidazo[1,2-*b*]-*s*-triazole **279**^{268b} and its conjugated acid **343**,^{268b} pyrazolo[1,5-*b*]-*s*-triazole,^{268b} imidazo[2,1-*c*]-*s*-triazole and its conjugated acid **344** (Section IV,C,1,b).^{268b} In the case of *s*-triazolo[3,4-*b*]benzothiazoles **182**, calculations have been effected using *sp* and *spd* approximations.⁴³⁵ Other azapentalenes, including tetrazole derivatives **185**, have also been examined,⁴³⁵⁻⁴³⁷ and some general results emerging from these CNDO studies are worth elaborating:

i. In accord with Trinajstić's model⁴³⁰ there is a correlation between the energies of different tautomers and their ionization potentials.^{268, 433}

ii. If net π -charges are examined by the CNDO/2 method, it appears that the five-membered ring bearing the heteroatom X (NH, O, S) is positively charged while the other ring carries an excess of electrons. As an example, the three tautomers of imidazo[1,2-*b*]-*s*-triazole **279** are shown in Scheme 22.^{268b, 437}



SCHEME 22

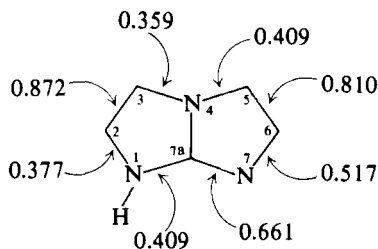
iii. An examination of π -bond orders shows that the five-membered ring containing the heteroatom X (NH, O, S) has a more localized π -system (e.g., imidazo[1,2-*a*]imidazole, Scheme 23).^{436, 437}

From a theoretical point of view, type C azapentalenes attracted interest a number of years ago through the fact that they are written with dipolar valence-bond structures. 3a,6a-Diazapentalene **262**, was studied first by Hückel's method,³⁴⁶ then later in more detail by PPP and

⁴³⁵ J. P. Fayet, M. C. Vertut, P. Mauret, R. Faure, J. P. Galy, E. J. Vincent, and J. Elguero, *Bull. Soc. Chim. Fr.* 288 (1977).

⁴³⁶ R. M. Claramunt, Thesis, Montpellier (1976).

⁴³⁷ R. Faure, E. J. Vincent, R. M. Claramunt, and J. Elguero, *Org. Magn. Reson.* **9**, 508 (1977).



SCHEME 23

CNDO/2 methods,⁴³⁴ giving charges, MO energies, and ionization potentials.

Two groups of Italian workers used the PPP method with configurational interactions to study polyazapentalenes. Vaciago *et al.*,⁴³⁸ using experimentally determined geometries^{351, 390} (Section V,A), calculated electronic transitions (Section V,E) in 1,3a,4,6a-tetraazapentalene **263** and showed that the introduction of penetration integrals is necessary for correct prediction of the sequence of N—N bond lengths based on the sequence of bond orders. Galasso *et al.*⁴³⁹ took up the study of this molecule along with other mono-, di-, tri-, and tetraazapentalenes by extending the configuration interaction (CI) treatment to all singlet monoexcited electronic configurations. These calculations satisfactorily predict electronic spectra, but predictions of reactivity based on ground-state electron densities do not always correspond with experiment.

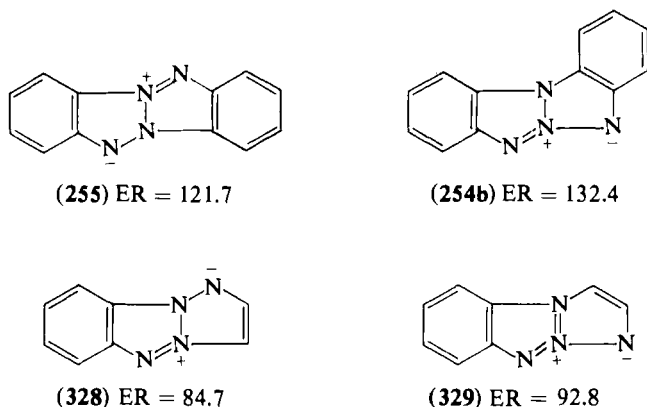
Chia and Simmons³⁸⁸ calculated the resonance energies (ER)²⁰ of four mono- and dibenzotetraazapentalenes (Scheme 24). Values are comparable with those of *o*-condensed aromatic systems (naphthacene, ER = 110 kcal mol⁻¹; chrysene, ER = 116.5 kcal mol⁻¹), and, like these carbocyclic systems, “angularly-shaped” molecules are more stable than “linear” ones. HMO calculations of delocalization energies (DE) show that the tetraazapentalene structure **15** is more stable than the tetraazacyclooctatetraene valence isomer **324** (Scheme 14, Section IV,B,2) whether **324** is planar or tub-shaped. Calculations of electrophilic reactivity (Section IV,C,4,d), electronic spectra (by the PPP method employing all singly excited configurations), and bond orders have been carried out, and they confirm the aromatic nature of these systems.

Tsuge and Samura³⁹² used the reactivities of positions 7 and 2 toward electrophiles calculated from frontier electron densities and superdelocalizabilities to assign the structures of disubstituted derivatives

⁴³⁸ L. Paoloni, P. Gramaccioni, and A. Vaciago, *Theoret. Chim. Acta* **5**, 102 (1966).

⁴³⁹ V. Galasso and G. De Alti, *Theoret. Chim. Acta* **11**, 411 (1968).

(Section IV,C,4,d) of 8-substituted dibenzo[*b,e*]-1,3a,6a-triazapentalene (**332b**).



SCHEME 24

C. DIPOLE MOMENTS

Most work has been done by the same group of workers,^{360, 363, 364, 367, 433, 435, 440} and practically all examples are from type B systems except for a study of the annular tautomerism (Section IV,A,1) of 4-methyl-6-phenylpyrazolo[3,4-*d*]-*v*-triazole (**90**),³⁶⁷ a type A system. Values shown here are expressed in Debyes (D), using dioxane as solvent.

For 2-methyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (**350**) and 4-methyl-*s*-triazolo[3,4-*b*]benzothiazole (**182**, R = Me), dipole moments were found to be 4.96 and 5.98, respectively.⁴³⁵ For compounds containing only nitrogen as a heteroatom, dipole moment measurements have been used to study annular tautomerism (Section IV,A,1) using Eq. (36).³⁵⁶

$$K_T = (\mu_B^2 - \mu_X^2)/(\mu_X^2 - \mu_A^2) \quad (36)$$

where μ_A and μ_B are the dipole moments of each tautomeric form and μ_X is the experimentally determined value for the mixture. Measurements of μ_X at 25°C and 45°C have enabled the position of equilibrium as a function of temperature to be found. Since μ_A and μ_B cannot be found experimentally, calculated values for each tautomer (from CNDO/2 or CNDO/S calculations, Section V,B) or experimentally determined

⁴⁴⁰ J. P. Fayet, M. C. Vertut, P. Mauret, E. Alcalde, and R. M. Claramunt, unpublished results.

values for *N*-methyl derivatives have been used. Using this method, the error in each variable has been estimated as <0.4 D. The correspondence between calculated and experimental values for *N*-methyl derivatives is sufficiently close to enable the structures of *N*-methyl derivatives (i.e., the position of methylation, Section IV,C,2) to be determined by comparing experimentally found values with those calculated for each tautomer.^{364, 367} This method has been applied to the following methyl derivatives: 6-methylimidazo[1,2-*b*]pyrazole (**276**) ($\mu_{25} = 4.13$),^{360, 433} *s*-triazolo[4,3-*b*]-*s*-triazole (**278**) ($\mu_{25} = 1.86$),^{364, 433} 2-methylpyrazolo[1,5-*a*]benzimidazole (**275**; R = Me) ($\mu_{25} = 3.75$),³⁶³ 3-methyl-*s*-triazolo[4,3-*a*]benzimidazole (**280**) ($\mu_{25} = 3.20$),³⁶³ and 6-methylpyrazolo[3,2-*c*]-*s*-triazole (**277**; R¹ = H; R² = Me) ($\mu_{25} = 2.58$).³⁶⁰ When more than two tautomers are possible, certain assumptions have to be made, or other physicochemical methods used, if K_T is required.

Dipole moment studies can give information on the position of azide \rightleftharpoons tetrazole equilibria (Section IV,B,1) with the limitation that model systems cannot be prepared and calculations have to be used.^{435, 440} Equilibrium constants obtained in this way are comparable with those obtained by NMR (Section V,G,2).

Among type C azapentalenes it has been shown³³⁹ that, of two dibenzotetraazapentalenes, the centrosymmetric isomer **255** has zero dipole moment, whereas the angular isomer **254b** has a moment of 4.36 D (benzene).

D. THERMODYNAMIC DATA

Using accurately measured heats of combustion (ΔH_c°) and sublimation (ΔH_{sub}), Chia and Simmons³⁸⁸ calculated heats of formation for four tetraazapentalenes (type C) referred to the gaseous form in standard states [$\Delta H_f^\circ(\text{g})$], and the following values were found: **255**, 142.8 ± 1.3 ; **254b**, 132.1 ± 1.5 ; **328**, 136.4 ± 1.2 ; **329**, 128.2 ± 1.3 (in kcal mol⁻¹). These results were used to calculate resonance energies (Section V,B).

E. ULTRAVIOLET SPECTRA

Table VI shows values of UV maxima for a number of simple azapentalenes, either unsubstituted or substituted with Me, Et, or CH₂Ph. In references^{335, 339} comparisons between the UV spectra of azapentalenes and homoaromatic substances are discussed.

The transitions observed are all $\pi \rightarrow \pi^*$ since $n \rightarrow \pi^*$ transitions are of higher energy and are masked by the tail of the $\pi \rightarrow \pi^*$ band.^{200, 438} Some

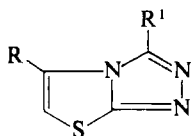
TABLE VI
ABSORPTION SPECTRA OF SIMPLE AZAPENTALENES

System	Compound	Solvent	Absorption [λ_{\max} in nm (log ϵ)]	Reference
<i>Type A</i>				
Thieno[3,2- <i>b</i>]pyrrole	460 : R = H	EtOH 95%	260(4.07)	431a
4-Benzylthieno[3,2- <i>b</i>]pyrrole	460 : R = CH ₂ Ph	EtOH 95%	267.5(4.08), 334(3.12)	431c
6-Benzylthieno[2,3- <i>b</i>]pyrrole	389 : R = CH ₂ Ph	EtOH 95%	250(3.99)	431b
5-Ethylthieno[2,3- <i>c</i>]pyrrole	89 : R = Et	EtOH 95%	236(4.08), 285(3.75)	84a
1,4-Dimethylpyrrolo[3,2- <i>b</i>]pyrrole	118	^a	260(4.24)	116
3-Methylpyrazolo[4,3- <i>c</i>]pyrazole	386	EtOH	223, 265(3.73)	66b
Imidazo[4,5- <i>d</i>]imidazole	80	MeOH	210(3.64), 242(3.79)	73b
<i>Type B</i>				
3a-Azapentalene anion	246	THF	210(4.30)(sh), 295 (3.98)	31a
1-Benzylpyrrolo[1,2- <i>a</i>]imidazole	373	EtOH 95%	285 ^b	32
6-Methylimidazo[1,2- <i>b</i>]pyrazole	276a	EtOH 95%	246.5(3.87)	245
2-Methylthiazolo[3,2- <i>b</i>]- <i>s</i> -triazole	414 : R ¹ = H, R ³ = Me	MeOH	206, ^c 242 ^c	143a
2,5-Dimethylthiazolo[3,2- <i>b</i>]- <i>s</i> -triazole	414 : R ¹ = R ³ = Me	MeOH	201(3.80), 246(3.91)	265
3-Methylthiazolo[2,3- <i>c</i>]- <i>s</i> -triazole	467 : R = Me, R ¹ = H	MeOH	204(3.75), 248(3.89)	265
6-Methylpyrazolo[3,2- <i>c</i>]- <i>s</i> -triazole	277 : R ¹ = H, R ² = Me	EtOH	205(4.01), 253(3.79)	162a
<i>s</i> -Triazolo[4,3- <i>b</i>]- <i>s</i> -triazole	278	MeOH	227(3.64) ^d	200
Imidazo[1,2- <i>b</i>]- <i>s</i> -triazole	279	EtOH 95%	227(3.46)	268b
2-Methylimidazo[2,1- <i>b</i>]benzothiazole	153b : R = Me	EtOH	242(4.15), 286(3.34), 294.5(3.17)	152a
Imidazo[2,1- <i>b</i>]benzoxazole	153c	EtOH	281.5(3.83)	152b
Thiazolo[3,2- <i>a</i>]benzimidazole	340	EtOH	250(3.76), 286(3.84) 293(3.94), 306(3.75)(sh)	256
2-Benzylimidazo[1,5- <i>a</i>]benzimidazole	468 : R ¹ = CH ₂ Ph; R ² = R ³ = H	^a	255(4), 330(3.8) ^e	126c

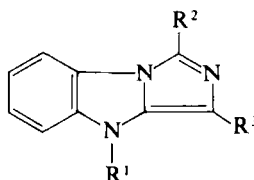
2-Methylpyrazolo[1,5- <i>a</i>]benzimidazole	275	EtOH	229(4.42), 306(4.01)	142
Benzimidazo[1,2- <i>b</i>]indazole	126	^a	266(3.7), 278(3.6), 306(3.5), 320(3.4)(sh), 340(3.3) ^e	123a
Benzimidazo[1,2- <i>a</i>]benzimidazole	177a : R = H	EtOH 95%	238(4.78), 285(4.25), 304(3.83)	167a
<i>s</i> -Triazolo[3,4- <i>b</i>]benzothiazole	415	MeOH	212(4.38), 220(4.34), 225(4.38), 244(4.03)(sh), 282(3.43), 289(3.14) ^f	186b
3-Methyl- <i>s</i> -triazolo[4,3- <i>a</i>]benzimidazole	280	MeOH	214(4.78), 232(4.29)(sh), 288 (3.69), 293(3.70) ^g	186b
Tetrazolo[5,1- <i>b</i>]benzothiazole	312b : R = H	MeOH	222(4.32), 240(4.0)(sh), 282 (3.83), 292(3.83)	186b
<i>Type C</i>				
3a,6a-Diazapentalene	262a	EtOH	284 ^b	346
2,6-Dimethyl-1,3a,4,6a-tetraaza- pentalene	263 : R ¹ = Me, R ² = H	MeOH	246(3.63), 279(4.18)	438
Dibenzo[<i>b</i> , <i>e</i>]-[1,3a,6a]triazapentalene	254a	^a	244(3.46), 262(3.62), 288 (3.30), 394(3.95)	335
Benzo[<i>b</i>]-1,3a,4,6a-tetraazapentalene	328	EtOH	236(4.44), 278(3.48), 343(4.34)	340
Benzo[<i>b</i>]-1,3a,6,6a-tetraazapentalene	329	EtOH	232(4.46), 285(3.58), 293(3.61), 326(4.18), 335(4.21)	336
Dibenzo[<i>b</i> , <i>f</i>]-[1,3a,4,6a]tetraaza- pentalene	255	EtOH	255(4.80), 308(3.45), 323(3.61), 364(3.89), 382(4.37), 402(4.58)	339
Dibenzo[<i>b</i> , <i>e</i>]-[1,3a,6,6a]tetraaza- pentalene	254b	EtOH	234(4.40), 271(3.77), 280 (3.92), 343(4.51), 356(4.60)	339

^a Solvent not indicated.^b Easily oxidized.^c Hygroscopic.^d in EtOH, 228 nm, (log ϵ = 3.61).³⁶⁴^e Value measured from published spectrum.^f In 95% EtOH spectrum is almost identical.⁴³⁵^g Spectrum is solvent dependent.^{195, 363}

publications deal with spectra determined in a range of solvents,^{162a, 245, 268b, 364} and in a few cases solvent effects have been correlated with the position of tautomeric equilibria.³⁶³ The effect of acid solvents has been mentioned earlier in connection with protonation^{139c, 268b, 364, 438} (Section IV,C,1). For the tetraazapentalene **263**, the fact that the UV spectrum is the same in EtOH/HCl and EtOH/KOH has been interpreted as indicating that the nitrogen lone pairs are more strongly bound in tetraazapentalenes than they are in pyridine, for instance (Section IV,C,1,a). The effect of substituents on spectra has been discussed for *s*-triazolo[3,4-*b*]benzothiazoles (**182**),^{186b} *s*-triazolo[4,3-*b*]-*s*-triazoles (**278**),^{124b, 200} thiazolo[3,2-*a*]benzimidazoles (**340**),⁴⁴¹ thiazolo[3,2-*b*]-*s*-triazoles (**414**),^{143a, 265} pyrrolo[1,2-*b*]-*s*-triazoles (**463**),^{289b} thiazolo[2,3-*c*]-*s*-triazoles (**467**),²⁶⁵ imidazo[1,5-*a*]-benzimidazoles (**468**),^{126a} dyes derived from imidazo[2,1-*b*]thiazole,³⁹⁷ phenyl-substituted heteropentalenes (**58**, **60**, **86a**, **86b**, **356a**),⁶³ and 1,2-diaryl-3a,6a-diazapentalenes (**262a**).³⁴³



(467)



(468)

F. INFRARED SPECTROSCOPY

Many azapentalenes have been characterized by their IR spectra, although these are frequently presented in an oversimplified manner (e.g., only C=C or C=N bands assigned). In this section, we shall discuss only specially significant results.

Azide \rightleftharpoons tetrazole equilibria (**184** \rightleftharpoons **185**, Section IV,B,1) in type B azapentalenes can be studied by IR. Azides show two characteristic vibration bands, an intense asymmetric vibration at 2100–2200 cm^{-1} and a symmetric band at 1200–1300 cm^{-1} . Often these bands appear as doublets or triplets.³⁸¹ Values for azide bands are reported for 3-azido- and 5-azidopyrazoles,^{185a, 187c, 442} 3-azidoindazoles,³⁶⁶ 2-azidoimidazoles,^{186d, 436} 2-azidobenzimidazoles,^{185a, 186c, 186d} 5-azidoimidazoles,⁴⁴² 3-azido-*s*-triazoles,^{124a, 192, 308, 436} 4-azido-*v*-triazoles,^{436, 442} 5-azidotetrazole,¹⁹¹ 2-azidothiazole,^{307a, 443, 444} 2-azidobenzothiazole,^{189a, 189b, 386} 2-

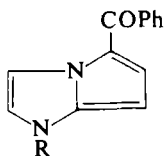
⁴⁴¹ V. A. Grin and N. G. Kras'yanenko, *Khim. Issled. Farm.* 18 (1970) [*CA* **76**, 52165 (1972)].

⁴⁴² Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.* **10**, 839 (1973).

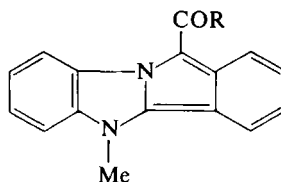
⁴⁴³ S. Maiorana and G. Pagani, *Chem. Ind. (Milan)* **53**, 470 (1971).

⁴⁴⁴ L. I. Skripnik and V. Y. Pochinok, *Khim. Geterotsikl. Soedin.* **4**, 474 (1968).

azidobenzoxazole,^{185a} 2-azido-1,3,4-thiadiazole,^{306a, 306b} 2-azido-naphtho[1,2-*d*]thiazole,^{188a} and 2-azidonaphtho[2,1-*d*]thiazole.^{188a} Tetrazoles are transparent in the region 2100–2200 cm^{-1} , but characteristic vibrations at 1110–1000 cm^{-1} (up to 3 bands), 763–758 cm^{-1} , and 741–735 cm^{-1} have been observed.⁴⁴⁵ IR data on azapentalenes with a tetrazole ring have been published for the following systems: thiazolo[3,2-*d*]tetrazole,^{185a, 307a} tetrazolo[5,1-*b*]benzothiazole,^{189a, b, 386} thiazolo[3,2-*d*]tetrazolium salts,^{41, 446, 447} pyrazolo[1,5-*d*]tetrazoles,³⁸² tetrazolo[5,1-*b*]naphtho[1',2'-*d*]thiazole,^{188a} and tetrazolo[5,1-*b*]naphtho[2',1'-*d*]thiazole.^{188a}



(469) $\nu_{\text{CO}} = 1602 \text{ cm}^{-1}$



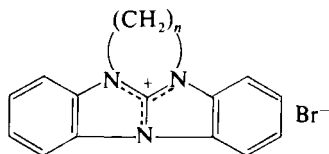
(470)

a: R = Me; $\nu_{\text{CO}} = 1531 \text{ cm}^{-1}$

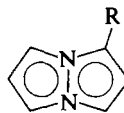
b: R = OMe; $\nu_{\text{CO}} = 1670 \text{ cm}^{-1}$

The unusually low frequencies of the carbonyl bands found in **469**³² and **470**³²² suggest that the C–O bond in these systems is considerably polarized. This implies that the molecules exist as “azulene-type” systems, i.e., the pyrrole ring donates and the imidazole ring receives a negative charge (cf. Section VII, and **276**, Section IV, A, 1).

Compound **471** ($n = 3$) possesses an abnormally high band at 1738 cm^{-1} , which has been attributed^{167b} to angular strain since compound **471** ($n = 4$) shows the corresponding band at much lower frequency (1668 cm^{-1}).



(471)



(262)

IR spectral data of many derivatives of thiazolo[3,2-*b*]-s-triazoles^{143a, 265} and thiazolo[2,3-*c*]-s-triazoles²⁶⁵ have been published.

There is little information on type A and type C azapentalenes.

⁴⁴⁵ E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.* **23**, 1594 (1951).

⁴⁴⁶ L. F. Avramenko, V. Y. Pochinok, and Y. S. Rozum, *Zh. Obshch. Khim.* **34**, 278 (1964).

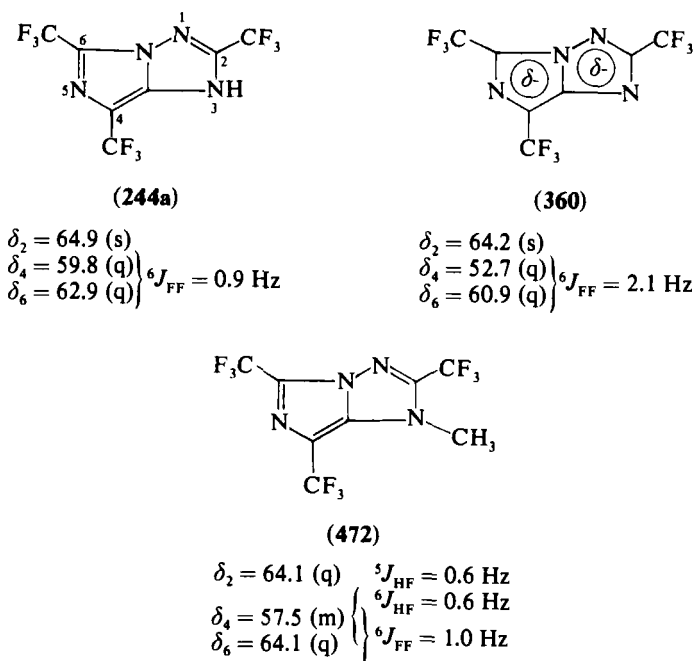
⁴⁴⁷ U. Askani, R. Neidlen, and J. Tauber, *Pharmazie* **26**, 463 (1971).

Trofimenko^{344, 347} comments that the IR spectrum of 3a,6a-diazapentalene (**262**, R = H) is consistent with a highly symmetrical structure (D_{2h}).

G. NUCLEAR MAGNETIC RESONANCE SPECTRA

Virtually all published work refers to proton magnetic resonance studies, though spectra of other nuclei are beginning to be examined. No ^{13}C studies have appeared so far (however, some unpublished measurements on type B systems have been made^{185b, 435, 437}).

The only reported ^{19}F study is that of Middleton and Metzger³²⁹ on 2,4,6-tris(trifluoromethyl)imidazo[1,5-*b*]-s-triazole and derivatives, and results are assembled in Scheme 25 (solvent: acetone; reference: CCl_3F).

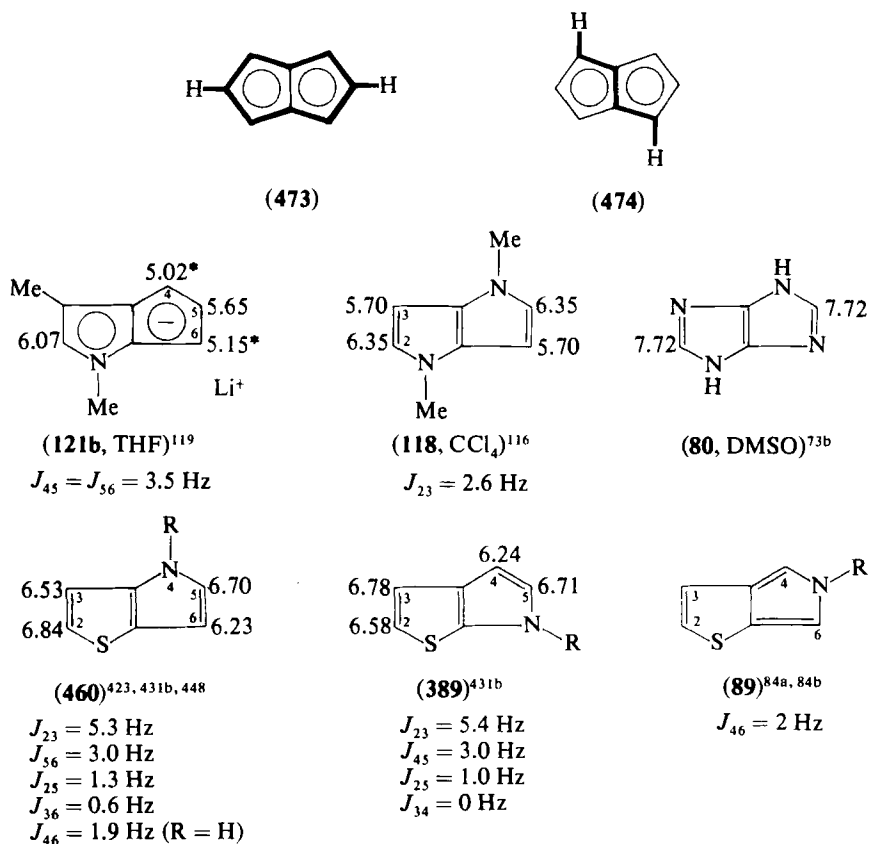


SCHEME 25

The increase in the value of ${}^6J_{\text{FF}}$ in passing from the neutral molecule **244a** to the anion **360** (tetramethylammonium salt) is worthy of note. The product obtained from methylation of **244a** with diazomethane (Scheme 16, Section IV,C,2) was assigned³²⁹ structure **472** (3-methyl), not **368** (1-methyl), on the basis of the ${}^6J_{\text{HF}}$ coupling constant.

1. Azapentalenes of Type A

Scheme 26 shows typical chemical shifts [in ppm with respect to tetramethylsilane (TMS) as internal standard] and coupling constants of protons attached to various azapentalenes. Since the chemical shifts of the protons in **121b** and **118** were not specified in the literature, we have assigned them by comparison with other published results (those marked * can be interchanged). Snyder *et al.* have published many data on thieno[3,2-*b*]pyrroles (**460**) and thieno[2,3-*b*]pyrroles (**389**); the chemical shifts shown in Scheme 26 correspond to *N*-benzyl derivatives ($R = CH_2Ph$).^{431b} We have reversed the published assignments of protons H_2 and H_3 in **389** because it seems more likely that the coupling of 1.0 Hz assumed to be between H_3 and H_5 is in fact between H_2 and H_5 . In all types of azapentalenes (A, B, and C), cross-ring coupling, **473** (1.2 ± 0.2 Hz) and zigzag coupling, **474** (0.7 ± 0.1 Hz), are seen.



SCHEME 26

⁴⁴⁸ R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.* **65**, 187 (1961).

From the spread (0.81–0.93 ppm) of chemical shifts of ortho and meta-para protons in a series of *N*-phenylazapentalenes (**58**, **60**, **86a**, **86b**, **356a**, **356b**), it was concluded⁶³ that the two rings were coplanar. This type of consideration, involving the influence of steric effects and the appearance of the phenyl group, has been applied to the different *N*-methyl isomers of 4-methyl-6-phenylpyrazolo[3,4-*d*]-*v*-triazole (**90**).⁸⁶

2. Azapentalenes of Type B

Since it is impossible to discuss the large amount of available information in a limited space, we have listed the published data on various systems, the most important references being marked with an asterisk.

Imidazo[1,5-*a*]benzimidazole (**406**),^{125, 398*} imidazo[2,1-*b*]benzothiazole (**401**),^{152a, 234} imidazo[5,1-*b*]benzothiazole (**404**),^{398*} imidazo[2,1-*b*]benzoxazole (**153c**),^{152b} imidazo[5,1-*b*]benzoxazole (**405**),^{398*} imidazo[1,2-*b*]pyrazole (**276**),^{40, 245, 362*} imidazo[1,2-*d*]tetrazole (**187d**),^{186d} imidazo[2,1-*b*]thiazole (**337**),^{225, 230*} imidazo[1,2-*b*]-*s*-triazole (**279**)^{244, 268b} (cation **343**^{268b}), imidazo[1,5-*b*]-*s*-triazole (**244a**),³²⁹ imidazo[2,1-*c*]-*s*-triazole (**165**)^{158b} (cation **344**^{268b}), isoindolo[2,1-*a*]-benzimidazole (**163**),³²² pyrazolo[1,5-*a*]benzimidazole (**275**),^{362*} pyrazolo[1,5-*d*]tetrazole (anion **306b**),^{187c} *N*-methyl derivatives, **307**, **308**^{366, 382, 436}), pyrazolo[3,2-*c*]-*s*-triazole (**277**),^{161a, 162a, 207, 268b} pyrrolo[1,2-*a*]-benzimidazole (**398**),^{281, 294, 310a} pyrrolo[1,2-*a*]imidazole (**373**),³² pyrrolo[1,2-*a*]pyrrole anion (**246**),^{31a} pyrrolo[2,1-*b*]thiazole (**19**),^{393*, 395*, 408, 409, 449} pyrrolo[1,2-*b*]-*s*-triazole (**463**),²⁸⁹ tetrazolo[1,5-*a*]benzimidazole (**304b**: X = S),^{186d} tetrazolo[5,1-*b*]benzothiazole (**312b**),³⁸³ thiazolo[3,2-*d*]tetrazole (**311b**),^{41, 307b} thiazolo[3,2-*a*]-benzimidazole (**340**),^{155, 256, 262a, 399a*} thiazolo[2,3-*c*]-*s*-triazole (**467**),²⁶⁵ thiazolo[3,2-*b*]-*s*-triazole (**414**),^{143, 265} *s*-triazolo[1,5-*a*]benzimidazole (**382**),²⁰³ *s*-triazolo[4,3-*a*]benzimidazole (**280**),^{195, 365} *s*-triazolo[3,4-*b*]-benzothiazole (**415**),^{435*, 450} *s*-triazolo[4,3-*d*]tetrazole (**181**),⁴⁵¹ *s*-triazolo[4,3-*b*]-*s*-triazole (**278**).^{202c, 364}

In general, chemical shifts and coupling constants have been obtained directly from spectra. Rigorous analyses of the ABCD system in some benzoazapentalenes have been undertaken;^{362, 365, 383, 450} cross-ring couplings,³⁶² nuclear Overhauser effect,³⁶⁵ and deuterium labeling⁴⁵⁰ have been used for the attribution. Coupling constants between “ortho” or “meta” protons on the same ring, or between protons and “ortho” methyl groups are close to those found for five-membered monocyclic

⁴⁴⁹ O. Ceder and B. Beijer, *Acta Chem. Scand.* **26**, 2977 (1972).

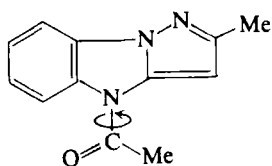
⁴⁵⁰ R. Faure, G. Giusti, J. P. Galy, E. J. Vincent, and J. Elguero, *Bull. Soc. Chim. Fr.*, 2967 (1974).

heterocycles.²³⁰ For the imidazo[2,1-*b*]thiazole (**337**), a comparison of $^3J_{23}$ and $^3J_{56}$ with the corresponding coupling constants for thiazole and *N*-alkylimidazoles enabled the authors²³⁰ to conclude that π -electron localization was greater in the thiazole ring.

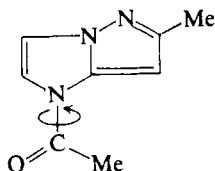
Coupling between CH and NH protons has enabled structures of annular tautomers (Section IV,A,1) to be resolved.^{245, 362} This unusual type of coupling has been associated with a loss of aromaticity of the five-membered ring which bears the NH³⁶² (a case where no $^1J(^1\text{H}-^{15}\text{N})$ coupling is seen has been reported elsewhere³²⁹). Cross-ring coupling of types **473**^{143b, 230, 268b} and **474**²⁰⁷ have been observed.

PMR spectra have frequently been used to solve structural problems including azide-tetrazole tautomerism (Section IV,B,1),^{185b, 186d, 187b, c, 307b, 308, 382, 383, 435} the site of C-protonation (Section IV,C,1,a)^{281, 393, 395} and *N*-protonation (Section IV,C,1,b),^{268b, 362} and the conformation of C-phenyl substituents.^{146, 451} The low-field displacement of chemical shifts by the introduction of a COR group into the molecule has frequently been noted,^{186d, 195, 203, 364, 365} and use has been made of this effect to study the site of *N*-acylation (Section IV,C,3).

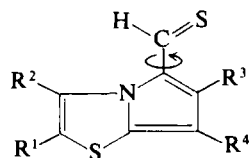
Restricted rotation in *N*-acetylated derivatives (**377**; **378**: $\Delta G^\ddagger = 61.5 \text{ kJ mol}^{-1}$)³⁶² and thioformyl derivatives **425**³⁹⁵ has been observed by NMR, and results have been correlated with an "azulene-type" model (see Section VII).



(377)



(378)



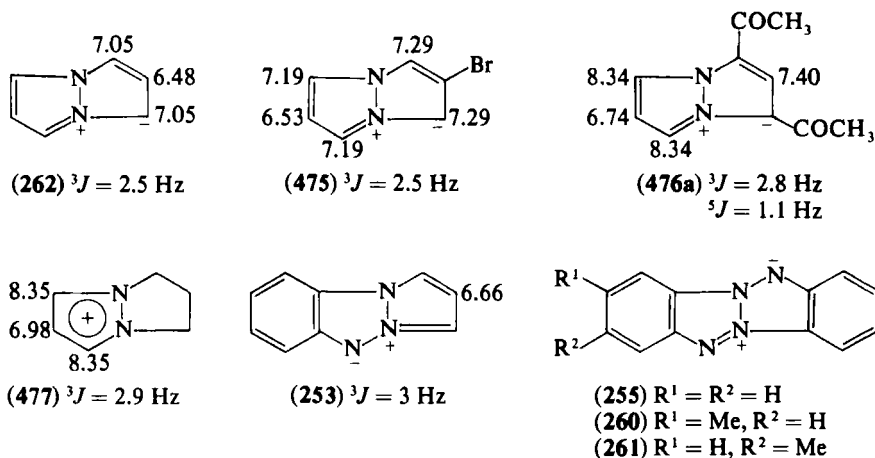
(425)

The use of lanthanide shift reagents⁴⁴⁹ and calculations on ring currents^{230, 398, 399a} have occasionally been reported.

3. Azapentalenes of Type C

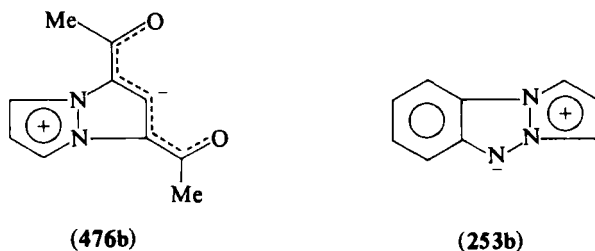
Solomons and Voigt^{345, 346} and Trofimenko^{344, 347} simultaneously published NMR data on 3a,6a-diazapentalene (**262**) and derivatives (Scheme 27).

⁴⁵¹ R. N. Butler, *Can. J. Chem.* **50**, 1786 (1972).



SCHEME 27

From these results, a comparison between the data for the diacetylated derivative **476a** and the pyrazolium salt **477** is particularly worthy of note, since the close similarity (J and δ) between the values for the pyrazole ring protons in these systems led to the conclusion that structure **476b** with the positive charge localized in the pyrazole ring is the best representation of **476a**.³⁴⁷ By analogy, **253b** may be proposed as the best representation of **253**, since this accounts for the proton observed at 6.66 ppm coupled to two other "pyrazole" protons with $J = 3$ Hz.^{333a}



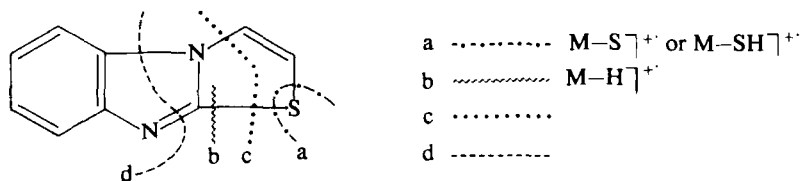
From the fact that the ABCD system of dibenzotetraazapentalene **255** did not become an AA'BB' system on heating, even at 225°C, it was concluded³³⁹ that the valence isomerization: tetraazapentalene = tetraazacyclooctatetraene (Scheme 14, Section IV,B,2) did not occur. Hall, Stephanie, and Nordstrom³⁴¹ have effected an analysis of the ABCD system of **255** and revealed the presence of two superimposed ABCD systems that give the molecule an element of symmetry. Chemical shifts conformed to electron densities calculated by Chia and Simmons (Section V,B,3).³⁸⁸ The same authors also studied the ABCD-

XYZ systems of **260** and **261** and found that the introduction of a methyl group perturbs the chemical shifts of the benzene ring protons some distance away. The transmission of this effect through many bonds led to the conclusion that these systems possessed aromatic character.³⁴¹ The analysis of the ABCD system of **254b** has also been performed by Hall.⁴⁵²

H. MASS SPECTROMETRY

Comparatively little work has been reported, and only a few type B systems have been studied in depth. For thiazolo[2,3-*c*]-*s*-triazoles (**467**)²⁶⁵ and thiazolo[3,2-*b*]-*s*-triazoles (**414**),^{143a, 265} the most intense peak corresponds to $[M - 1]^+$ and fragmentation begins with the *s*-triazole ring. Certain workers²⁶⁵ have stressed the dangers inherent in using mass spectrometry for structural assignments since different systems can yield similar fragmentation patterns. The mass spectra of derivatives of imidazo[1,2-*b*]pyrazole (**409**)^{146, 245} show a very intense molecular ion peak and few other peaks; this reflects the stability of the ring system. For thiazolo[3,2-*a*]benzimidazole (**340**), four main fragmentations have been proposed²⁵⁹ (a, b, c, d in Scheme 28), and the same workers report that imidazo[2,1-*b*]benzothiazoles (**401**) behave analogously, whereas imidazo[2,1-*b*]thiazoles (**400**) do not display type a fragmentation.²⁵⁹ There is some information on the mass spectra of thiazolo[3,2-*d*]tetrazolium salts (**28**)⁴¹ and azido-*s*-triazoles (isomers of triazolotetrazoles).³⁰⁹ For a paper dealing with mass spectrometry of pyrrolo[1,2-*a*] benzimidazoles and imidazo[1,2-*a*]benzimidazoles see reference 399b.

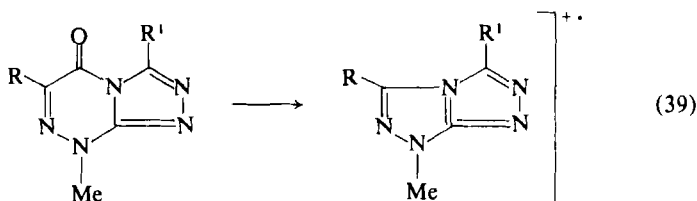
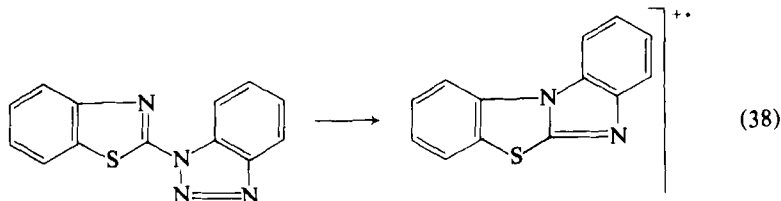
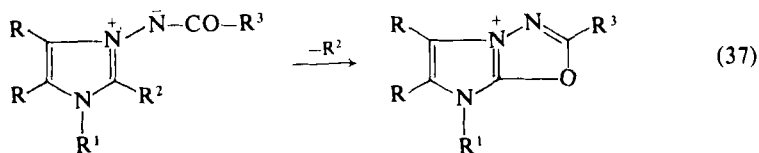
Azapentalene systems have been proposed as fragments in the mass spectra of certain heterocycles, e.g., in Eqs. (37),^{453a} (38),^{169a} and (39).^{453b}



SCHEME 28

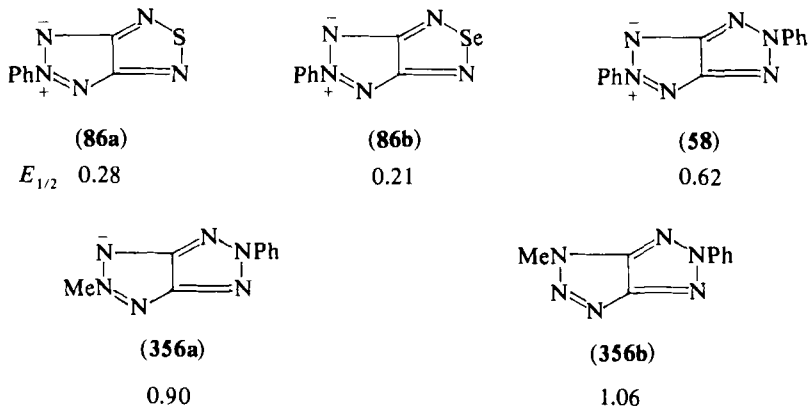
⁴⁵² J. H. Hall, *J. Org. Chem.* **36**, 217 (1971).

⁴⁵³ (a) Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 781 (1974); (b) M. Follet, Thesis, Montpellier (1976).



I. POLAROGRAPHY

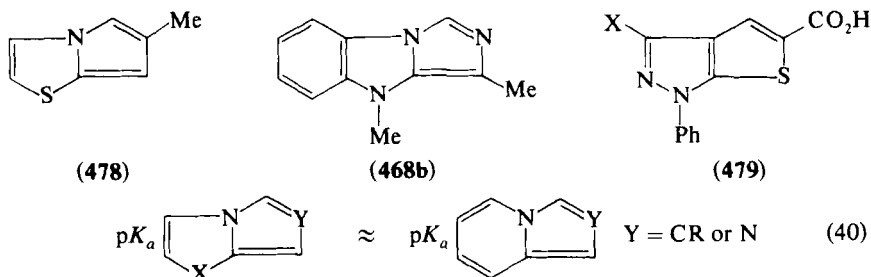
Matsumoto, Yoshida, and Simamura⁶³ have measured the half-wave reduction potentials ($E_{1/2}$) for the first wave in DMF for a number of type A azapentalenes (Scheme 29). As shown the values for **86a** and **86b** are strikingly higher than those of the hexaazapentalenes **58**, **356a**, and **356b**. This difference has been attributed⁶³ to the effect of replacing nitrogen with sulfur or selenium. The difference between the values for the symmetric mesoionic system **58** and its two methyl derivatives, **356a** and **356b**, is also worthy of note.



SCHEME 29

J. ACID-BASE STRENGTH

Little work has been reported. From studies of proton/deuterium exchange rates, 2-methylpyrrolo[2,1-*b*]thiazole (**478**) was estimated to have a pK_a of 6.4,³⁹⁴ a value comparable with that of 2-methylindolizine ($pK_a = 5.9$).³⁹⁴ In the same way, the basicity of 3,4-dimethylimidazo[1,5-*a*]benzimidazole (**468b**) ($pK_a = 6.01$) resembles that of imidazo[1,2-*a*]pyridines ($pK_a = 5.05$ – 5.96).³⁹⁸ It would seem, therefore, that the basicity of azapentalenes parallels that of related indolizine derivatives [Eq. (40)].



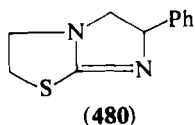
A study of the pK_a 's of a series of 1-phenylthieno[2,3-*c*]pyrazole-carboxylic acids with different 3-substituents (**479**) showed that substituent effects in bicyclic type A systems are transmitted less strongly ($\rho = 1.17$) than in the corresponding benzo[*b*]thiophenes ($\rho = 2.5$).⁹⁴

The basicity of the 3a-azapentalene anion (**246**) ($pK_a \approx 29$)^{31a} has been discussed earlier (Section V,B).

VI. Uses and Applications

A. BIOLOGICAL ACTIVITY

Table VII lists biological activities that have been found for some aromatic azapentalenes. Among these, imidazo[2,1-*b*]thiazoles have probably been most studied, and this has partly followed the discovery⁴⁵⁴ that a tetrahydro derivative **480** possessed marked anthelmintic activity. This compound is marketed as Tetramisole (or as the L-isomer, Levamisole) and is at present one of the most effective agents for the treatment of roundworm infestations. Anthelmintic activity has been found for aromatic imidazo[2,1-*b*]thiazoles (Table VII), and it has been suggested²³¹ that a 6-aryl substituent is necessary for activity in this series.



⁴⁵⁴ A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. S. A. Demoen, T. T. T. Van Offenwert, and P. A. J. Janssen, *J. Med. Chem.* **9**, 545 (1966).

TABLE VII
BIOLOGICAL ACTIVITY OF AROMATIC AZAPENTALENES

System	Derivatives	Biological activity	References
Thieno[2,3- <i>d</i>]imidazole	2-Thiazolyl	Anthelmintic	52
Imidazo[4,5- <i>d</i>]thiazole	Various	Analgesic, antispastic	455
Pyrrolo[2,3- <i>c</i>]pyrazole	4,5-Ar ₂	Analgesic, antipyretic	69, 111
Thieno[2,3- <i>c</i>]pyrazole	5-COR	Antiamoebic	96
Thieno[3,2- <i>b</i>]pyrrole	5-CONR ¹ R ²	Antidepressant	456
Thiazolo[5,4- <i>d</i>]thiazole	2,5-Ar ₂	Antiprotozoal	457
	Various	Antiparasitic	457
	Various	Hypocholesteremic	457
	2,5-Cl ₂	Insecticidal	459
Pyrazolo[3,4- <i>c</i>]isothiazole	3-NH ₂ , 6-Ar	Antifungal	71
Thieno[2,3- <i>b</i>]indole	2-Ar	CNS depressant	76
Thieno[3,2- <i>b</i>]indole	3-CONR ¹ R ²	Antihistaminic	458
Indeno[1,2- <i>c</i>]pyrazole	Various	Tranquilizing	67
Benzothieno[3,2- <i>b</i>]indole	Various	Antihistaminic	105b
	2,8-Diamidine	Trypanocidal	106
Imidazo[2,1- <i>b</i>]thiazole	3,6-Diaryl	Antihistaminic	460
	6-Cl	Anti-inflammatory	461
	6-Thienyl	Anti-inflammatory	462
	6-Benzimidazole	Anthelmintic	463
	6-Ph, 6-Ar	Anthelmintic	231, 464
	5-SCN	Antifungal, antiviral	465
	5,6-Dianisyl	CNS stimulant	467

	6-Me	Anti-inflammatory	466
	Salts	Hypoglycemic	468
	Various	Antibacterial, antifungal	469
	6-Ar	Anticonvulsant	208
Thiazolo[3,2- <i>a</i>]benzimidazole	2-Br	Antifungal	471
Imidazo[2,1- <i>b</i>]benzothiazole	3-NO ₂ , Hal, SCN	Plant antiviral	472
Thiazolo[2,3- <i>c</i>]- <i>s</i> -triazole	2-Furyl	Hypotensive	266
<i>s</i> -Triazolo[3,4- <i>b</i>]benzothiazole	Various	Pesticidal, antifungal	473
[1,2,4]-Thiadiazolo[2,3- <i>a</i>]benzimidazole	2-Ar, 2-hetaryl	Antifungal	474
Imidazo[2,1- <i>b</i>]1,2,4-thiadiazole	2-Ar, 2-hetaryl	Antifungal	475
	5-SCN	Antibacterial, antiviral	482
1,2,4-Thiadiazolo[4,5- <i>a</i>]benzimidazole	1-Imidazolyl	Antifungal	476
Thiazolo[3,2- <i>b</i>]- <i>s</i> -triazole	2-Phosphorothioate	Anthelmintic	477
	2-Phosphorothioate	Insecticidal	202e, 478
	2-Ar	Antiparasitic	479
	6-OCONMe ₂	Insecticidal	480
	6-Br, 5-Me	Antibacterial	481
	2-Furyl	Hypotensive	266
Imidazo[1,2- <i>a</i>]benzimidazole	2-Ar	Antibacterial, antiviral	483
	Various	Sedative, hypotensive	218, 484
Pyrazolo[1,5- <i>a</i>]benzimidazole	Various	CNS stimulant	141e, 141g
Imidazo[2,1- <i>b</i>]oxazole	5,6-dianisyl	CNS stimulant	467
	Various	Antiviral	485
Imidazo[2,1- <i>a</i>]isoindole	5-Ar	CNS stimulant, anorectic	131, 133
Pyrrolo[2,1- <i>a</i>]isoindole	2-Ar	Herbicide, plant growth regulator	486
Pyrazolo[5,1- <i>b</i>]thiazole	3-NO, 2-Me	Antibacterial	205

Aromatic azapentalenes have not been found naturally, though an imidazo[4,5-*d*]imidazole derivative has been implicated in the prebiotic synthesis of purines^{73c, 74} (see also Section III,A,1,d). Saturated derivatives occur fairly widely; the *Senecio* alkaloids contain the reduced pyrrolo[1,2-*a*]pyrrole (pyrrolizidine) skeleton,⁴⁸⁷ and the alkaloid withasomnine is a derivative of pyrrolo[1,2-*b*]pyrazole.^{374, 488} The mitomycin antibiotics mentioned earlier in this review (Sections III,B,1,f and III,B,5) contain the pyrrolo[1,2-*a*]indole ring,^{166, 331} and the recently reported fungal metabolite sporidesmin is a saturated derivative of pyrrolo[2,3-*b*]indole.⁴⁸⁹

B. PHOTOGRAPHIC USES

Aromatic azapentalenes feature in a number of patents dealing with color couplers, sensitizing dyes, and emulsion stabilizers (see also Section IV,C,4,b). Derivatives of pyrazolo[1,5-*a*]benzimidazoles^{139b,c,d,e,f, 140a,b, 419, 490} have been patented by Agfa as color couplers

⁴⁵⁵ Shionogi and Co., Japanese Patent 7,031,944 (1970).

⁴⁵⁶ H. J. Brabander and W. B. Wright, U.S. Patent 3,706,810 (1972) [CA 78, 84422 (1973)].

⁴⁵⁷ Ciba Ltd., Netherland Patent 6,515,334 (1966) [CA 65, 15409 (1966)].

⁴⁵⁸ L. H. Werner, U.S. Patent 3,151,120 (1964) [CA 61, 14677 (1964)].

⁴⁵⁹ D. Beck and H. Holtschmidt, German Patent 2,214,610 (1972) [CA 79, 146509 (1973)].

⁴⁶⁰ M. Patra, S. K. Mahapatra, and B. Dash, *J. Indian Chem. Soc.* 51, 1031 (1974).

⁴⁶¹ J. P. Paolini and L. J. Lendvay, *J. Med. Chem.* 12, 1031 (1969).

⁴⁶² M. Tanaka, K. Otsuka, M. Obata, T. Tanabe, T. Saida, K. Nomura, K. Amenija, K. Saga, and S. Kano, Japanese Patent 7,470,986 (1974) [CA 81, 136142 (1974)].

⁴⁶³ Chimetron S. A. French Patent 1,488,270 (1967) [CA 69, 59248 (1968)].

⁴⁶⁴ Y. Hashimoto and S. Kano, Japanese Patent 7,319,715 (1973) [CA 79, 61794 (1973)].

⁴⁶⁵ S. Kano, D. Takiguchi, and T. Noguchi, Japanese Patent 6,824,187 (1968) [CA 70, 57839 (1969)].

⁴⁶⁶ Sankyo Co., Belgium Patent 660,274 (1965) [CA 63, 18103 (1965)].

⁴⁶⁷ D. Lednicer, U.S. Patent 3,455,924 (1969) [CA 71, 101878 (1969)].

⁴⁶⁸ D. E. Kuhl, U.S. Patent 3,860,718 (1975) [CA 82, 140133 (1975)].

⁴⁶⁹ W. Weuffen, T. Pyl, W. Grübner, and W-D. Jülich, *Pharmazie* 20, 629 (1965); G. Tartler and W. Weuffen, *ibid.* 21, 425 (1966).

⁴⁷⁰ N. Saldabols, S. Hillers, L. N. Alekseeva, and B. Brizga, *Khim. Farm. Zh.* 1, 27 (1967) [CA 68, 2856 (1968)].

⁴⁷¹ S. Kano and T. Noguchi, Japanese Patent 7,338,720 (1973) [CA 81, 3944 (1974)].

⁴⁷² T. Noguchi and S. Kano, Japanese Patent 6,811,915 (1968) [CA 69, 106709 (1968)].

⁴⁷³ C. J. Paget, German Patent 2,250,077 (1973) [CA 79, 18721 (1973)].

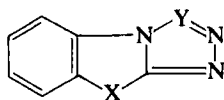
⁴⁷⁴ C. C. Beard (Syntex Ltd.) U.S. Patent 3,901,903 (1975) [CA 84, 17364 (1976)].

⁴⁷⁵ C. C. Beard (Syntex Ltd.) U.S. Patent 3,946,031 (1976) [CA 85, 21381 (1976)].

⁴⁷⁶ R. D. Haugwitz, U.S. Patent 3,864,353 (1975) [CA 82, 156323 (1975)].

for magenta dyes, and pyrazolo[3,2-*c*]-*s*-triazoles have been patented by Kodak⁴⁹¹ for the same purpose. Pyrazolo[1,5-*a*]-benzimidazoles have been patented as developers.^{139a} Condensation products of some systems with aldehydes have been claimed as sensitizing dyes; these include: pyrazolo[5,4-*d*]thiazoles,^{80a} pyrazolo[1,5-*a*]benzimidazoles,⁴¹⁹ thiazolo[4,5-*d*]thiazoles,^{492, 492a} thiazolo[3,2-*a*]benzimidazoles,⁴⁹³ and pyrazolo[3,2-*c*]-*s*-triazoles.¹²⁹ Azo dyes from this last-named system are claimed as filter dyes,^{129a} and thiazolo[5,4-*d*]thiazoles^{492a} are patented as fluorescent whitening agents.⁴⁹⁴ Derivatives of systems **481** are patented as emulsion stabilizers and antifoggants.^{196a,b, 495}

- ⁴⁷⁷ S. Kano, O. Nomura, and T. Taniguchi, Japanese Patent 7,368,589 (1973) [CA **80**, 37118 (1974)]; S. Kano, Y. Hashimoto, and Y. Arima, Japanese Patent 7,368,720 (1973) [CA **80**, 44714 (1974)].
- ⁴⁷⁸ S. Kano, O. Nomura, M. Asada, M. Ando, and M. Michihiko, German Patent 2,264,162 (1973) [CA **80**, 3531 (1974)]; S. Kano, O. Nomura, and T. Taniguchi, Japanese Patent 7,375,589 (1973) [CA **80**, 70812 (1974)].
- ⁴⁷⁹ S. Kano and T. Noguchi, Japanese Patent 7,137,836 (1971) [CA **76**, 25295 (1972)].
- ⁴⁸⁰ H. Hoffmann and I. Hammann, German Patent 2,032,173 (1972) [CA **76**, 72525 (1972)].
- ⁴⁸¹ S. Kano and T. Noguchi, Japanese Patent 7,126,498 (1971) [CA **75**, 140864 (1971)].
- ⁴⁸² S. Kano and T. Noguchi, Japanese Patent 7,126,514 (1971) [CA **75**, 14065 (1971)].
- ⁴⁸³ H. Ogura, German Patent 2,003,825 (1970) [CA **74**, 53787 (1971)].
- ⁴⁸⁴ S. V. Ivanovskaya, *Sb. Nauch. Rab. Volgograd. Gos. Med. Inst.* **22**, 139 (1969) [CA **75**, 47311 (1971)]; **22**, 142 (1969) [CA **75** 33574 (1971)]; **21**, 175 (1968) [CA **74**, 51876 (1971)]; A. M. Simonov, A. A. Belous, V. A. Anisimova, and S. V. Ivanovskaya, *Khim. Farm. Zh.* **3**, 7 (1969) [CA **71**, 81267 (1969)].
- ⁴⁸⁵ T. Ito, S. Sugimoto, and H. Ogura, Japanese Patent 7,116,750 (1971) [CA **75**, 36030 (1971)].
- ⁴⁸⁶ H. Sugihara, N. Matsumoto, Y. Hamuro, and Y. Kawamatsu, *Arzn. Forsch.* **24**, 1560 (1974).
- ⁴⁸⁷ N. K. Kotchetkov and A. W. Likhoshesterov, *Adv. Heterocycl. Chem.* **5**, 315 (1965).
- ⁴⁸⁸ H-B. Schröter, D. Neumann, A. R. Katritzky, and F. J. Swinbourne, *Tetrahedron* **22**, 2895 (1966).
- ⁴⁸⁹ H. J. C. Ottenheijm, J. A. M. Hulshof, and R. J. F. Nivard, *J. Org. Chem.* **40**, 2147 (1975).
- ⁴⁹⁰ Fuji Photo Film Co. Ltd., German Patent 2,156,111 (1972) [CA **77**, 101610 (1972)].
- ⁴⁹¹ Eastman Kodak Ltd., Belgium patent 792,525 (1975).
- ⁴⁹² Shostku Chemical Photo Ind. Ltd., USSR Patent 690,001 (1975).
- ⁴⁹² (a) Strictly these systems are outside the scope of this review (Section II,C,2), because they possess two sulfur atoms.
- ⁴⁹³ E. J. Poppe, German (East) Patent 49,396 (1966).
- ⁴⁹⁴ K. M. Dear, R. A. Jeffreys, and D. A. Thomas, U.S. Patent 3,630,738 (1971) [CA **76**, 142409 (1972)].
- ⁴⁹⁵ E. T. Smith and L. L. Williams, British Patent 931,293 (1963) [CA **59**, 9496 (1963)].



(481)

X = O, S, NH

Y = N, CR

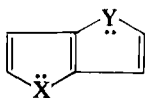
C. OTHER USES

Derivatives of various systems are patented as azo dyes: pyrazolo-[1,5-*a*]benzimidazoles,^{141a-d,f,h} isoindolo[2,1-*a*]benzimidazoles,^{321a-c} and imidazo[2,1-*b*]thiazoles.³⁹⁷ Benzothieno and benzofuro[2,3-*d*]-*v*-triazolyl coumarins are claimed as fluorescent whitening agents,^{97, 98} and benzo[*b*]-1,3a,4,6a-tetraazapentalenes³³⁸ and dibenzo[*b,e*]-1,3a,6,6a-tetraazapentalenes³³⁷ as UV absorbers and sunscreens agents. Since 3a,6a-diazapentalenes give dark products with oxygen, they have been patented as oxygen estimators.³⁴⁹ The pyrrolo[1,2-*a*]imidazole skeleton occurs in various polymers.³²⁴

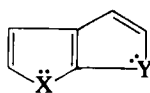
VII. General Conclusion

To conclude this article, a few generalizations about the aromaticity of azapentalenes (Section II) will be considered.

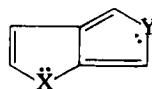
Type A systems seem to behave as two separate aromatic rings, since there is a good deal of evidence for a lack of interaction between the two parts. Compounds with a central double bond (e.g., **482** and **483**) are more stable than, for example, **484**, at least when one of the heteroatoms (X and Y) is sulfur [compare **282b** (Section IV,A,1) and **89** (Section V,B)]. Peri-interactions between free lone pairs can destabilize a system.



(482)



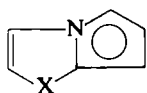
(483)



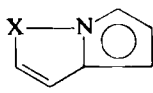
(484)

Type B azapentalenes behave as one ring, but aromatic character in systems such as **485** seems to be more localized in the ring that lacks the heteroatom X. The nature of X is important, since sulfur derivatives are the most stable; this is probably due to a reduction of angle strain and/or to the participation of *d*-orbitals. Physicochemical measurements, chemical reactivity, and quantum-mechanical calculations show

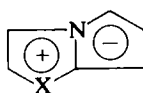
that an azulene-type model **486** adequately represents the π -system of this class of azapentalene.



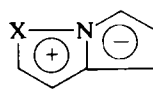
(485a)



(485b)

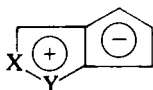


(486a)

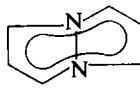


(486b)

When $X = \text{NH}$, the corresponding anions ($X = \text{N}^-$) are more aromatic than the conjugate acid. Type A azapentalenes in which two doublets are contributed by heteroatoms in the same ring are equally well represented by an azulene-type structure **487**.



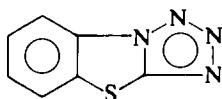
(487)



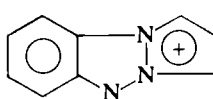
(488)

Only type C azapentalenes can accurately be represented by a delocalized π -system extending over both rings (**488**), and even this is not valid when electron-attracting substituents are present [e.g., **476b** (Section V,G,3)].

Certain benzo derivatives of type B and C systems seem to behave as a benzene ring and a heteroaromatic ring joined by bridge [e.g., **312a** (Section V,A), and **253b** (Section V,G,3)].



(312a)



(253b)

VIII. Index of Rings Covered in This Chapter

Azapentalenes of Type A

Benzofuro[3,2-*b*]indole: III,A,3,c

Benzofuro[3,2-*c*]pyrazole: III,A,3,b; III,A,4; IV,A,2,a

Benzofuro[2,3-*d'*]-*v*-triazole: VI, C

Benzothieno[2,3-*d*]imidazole: III,A,1,b; IV,A,1

Benzothieno[3,2-*b*]indole: III,A,1,a; III,A,3,c; VI,A

Benzothieno[3,2-*c*]pyrazole: III,A,1,a; III,A,3,d

Benzothieno[2,3-*b*]pyrrole: III,A,1,a
 Benzothieno[3,2-*b*]pyrrole: III,A,1,a; III,A,3,e; IV,C,4,a
 Benzothieno[2,3-*d*]-*v*-triazole: III,A,3,b; VI,C
 Cyclopenta[*b*]pyrrole (1-azapentalene): II,C,1; III,A,5; V,G,1
 Cyclopenta[*c*]pyrrole (2-azapentalene): III,A,5
 Furo[3,2-*b*]pyrrole: III,A,1,a; IV,D,2
 Imidazo[4,5-*d*]imidazole: III,A,1,d; IV,A,1; IV,F; V,E; V,G,1; VI,A
 Imidazo[4,5-*c*]pyrazole: III,A,1,d
 Imidazo[4,5-*d*]thiazole: IV,A,2,b; VI,A
 Indeno[1,2-*d*]isothiazole: III,A,5
 Indeno[1,2-*d*]isoxazole: III,A,5
 Indeno[1,2-*c*]pyrazole: III,A,1,d; VI,A
 Indeno[2,1-*c*]pyrazole: II,C,1; III,A,5; IV,A,1; IV,C,1,a; IV,C,2;
 IV,C,4,a
 Indolo[3,2-*b*]indole: III,A,1,b; IV,E; IV,F
 Isothiazolo[4,5-*b*]indole: III,A,2
 Isoxazolo[3,4-*c*]pyrazole: III,A,3,b
 Isoxazolo[4,5-*d*]-*v*-triazole: III,A,1,c; IV,A,1
 Pyrazolo[3,4-*b*]indole: III,A,3,d
 Pyrazolo[3,4-*c*]isothiazole: III,A,1,d; VI,A
 Pyrazolo[4,3-*d*]isoxazole: III,A,3,a
 Pyrazolo[3,4-*c*][1,2,5]oxadiazole: III,A,1,d
 Pyrazolo[3,4-*c*]pyrazole: III,A,3,a; III,A,3,b; IV,E
 Pyrazolo[4,3-*c*]pyrazole: III,A,1,c; III,A,4; IV,A,2,a; IV,C,1,a; IV,C,2;
 IV,C,4,a; IV,C,4,d; V,E; V,G,1
 Pyrazolo[3,4-*d*]thiazole: III,A,2; III,A,3,f; IV,A,2,a; IV,A,2,c; V,A
 Pyrazolo[4,3-*d*]thiazole: III,A,2
 Pyrazolo[3,4-*d*]-*v*-triazole: III,A,2; IV,A,1; IV,C,2; V,C; V,G,1
 Pyrrolo[2,3-*b*]indole: III,A,1,b; VI,A
 Pyrrolo[2,3-*c*]pyrazole: III,A,1,d; III,A,3,a; III,A,3,e; VI,A
 Pyrrolo[2,3-*b*]pyrrole: III,A,1,b; IV,A,1; IV,A,2,a
 Pyrrolo[3,2-*b*]pyrrole: III,A,1,a; III,A,4; IV,D,2; V,E; V,G,1
 [1,2,3]Thiadiazolo[5,4-*b*]indole: III,A,3,f
 Thiazolo[5,4-*b*]indole: III,A,2
 Thiazolo[4,5-*d*]thiazole: VI,B
 Thiazolo[5,4-*d*]thiazole: VI,A
 Thieno[2,3-*d*]imidazole: III,A,1,b; VI,A
 Thieno[2,3-*b*]indole: III,A,2; VI,A
 Thieno[3,2-*b*]indole: III,A,1,d; VI,A
 Thieno[2,3-*c*]pyrazole: III,A,3,a; IV,A,2,a; IV,C,4,a; IV,D,1; IV,D,2;
 V,J; VI,A
 Thieno[3,2-*c*]pyrazole: III,A,1,b
 Thieno[3,4-*c*]pyrazole: III,A,2
 Thieno[2,3-*b*]pyrrole: II,C,2; III,A,1,a; III,A,1,d; III,A,3,a; III,A,3,e;

IV,A,2,a; IV,C,4,a; IV,D,2; V,B; V,E; V,G,1
 Thieno[3,2-*b*]pyrrole: III,A,1,a; III,A,1,b; III,A,3,a; III,A,3,e; IV,C,4,a;
 IV,D,2; V,B; V,E; V,G,1; VI,A
 Thieno[2,3-*c*]pyrrole: III,A,2; III,A,3,f; V,B; V,E; V,G,2
 Thieno[3,4-*c*]pyrrole: III,A,2; V,B
v-Triazolo[4,5-*c*][1,2,5]oxadiazole: II,C,1; III,A,1,c; V,E
v-Triazolo[4,5-*c*][1,2,5]selenadiazole: III,A,2; V,E; V,G,1; V,I
v-Triazolo[4,5-*c*][1,2,5]thiadiazole: III,A,2; V,E; V,G,1; V,I
v-Triazolo[4,5-*d*]-*v*-triazole: III,A,1,c; IV,C,2; V,E; V,G,1; V,I

Azapentalenes of Type B

Benzimidazo[1,2-*a*]benzimidazole: III,B,1,g; IV,C,2; IV,F; V,E; V,F
 Benzimidazo[1,2-*b*]indazole: III,B,1,a; III,B,1,g; IV,A,1; V,E
 Benzimidazo[2,1-*b*]benzothiazole: III,B,1,g; V,H
 Imidazo[1,2-*a*]benzimidazole: III,B,1,f; III,B,1,g; III,B,2,a; III,B,3,a;
 III,B,3,e; IV,A,2,a; IV,C,2; IV,C,4,b; IV,C,4,c; IV,D,1; IV,D,2;
 IV,E; V,B; V,H; VI,A
 Imidazo[1,5-*a*]benzimidazole: III,B,1,b; IV,C,1,b; IV,C,4,b; IV,C,4,c;
 IV,D,2; V,B; V,E; V,G,2; V,J
 Imidazo[2,1-*b*]benzothiazole: III,B,1,e; III,B,3,a; IV,C,4,b; IV,C,4,c;
 V,E; V,G,2; V,H; VI,A
 Imidazo[5,1-*b*]benzothiazole: III,B,1,b; IV,C,4,b; IV,C,4,c; IV,D,1;
 IV,D,2; V,B; V,G,2
 Imidazo[2,1-*b*]benzoxazole: III,B,1,e; III,B,3,a; V,E; V,G,2
 Imidazo[5,1-*b*]benzoxazole: IV,C,4,b; IV,C,4,c; IV,D,1; IV,D,2;
 IV,E; V,B; V,G,2
 Imidazo[1,2-*a*]imidazole: III,B,1,b; III,B,2,a; III,B,3,a; IV,C,1,b;
 IV,F; V,B
 Imidazo[1,5-*a*]imidazole: III,B,3,c
 Imidazo[2,1-*a*]isoindole: III,B,1,b; III,B,3,e; III,B,4,a; VI,A
 Imidazo[2,1-*b*]naphtho[2',1'-*b*]thiazole: III,B,3,a
 Imidazo[2,1-*b*][1,3,4]oxadiazole: III,B,1,b; III,B,3,a; IV,C,2; V,H
 Imidazo[2,1-*b*]oxazole: VI,A
 Imidazo[1,2-*b*]pyrazole: II,C,3; III,B,1,b; III,B,2,b; III,B,3,a; IV,A,1;
 IV,C,1,b; IV,C,2; IV,C,4,b; IV,F; V,B; V,C; V,E; V,G,2; V,H
 Imidazo[2,1-*b*][1,3,4]selenadiazole: III,B,3,a
 Imidazo[1,2-*d*]tetrazole: III,B,3,d; IV,B,1; IV,C,2; V,B; V,G,2
 Imidazo[2,1-*b*][1,2,4]thiadiazole: VI,A
 Imidazo[2,1-*b*][1,3,4]thiadiazole: III,B,3,a; IV,C,4,b; IV,C,4,c
 Imidazo[2,1-*b*]thiazole: III,B,1,b; III,B,3,a; IV,A,2,a; IV,A,2,c;
 IV,C,1,b; IV,C,2; IV,C,4,b; IV,C,4,c; IV,D,2; V,A; V,B; V,E;
 V,G,2; VI,A; VI,C
 Imidazo[5,1-*b*]thiazole: III,B,1,b; III,B,3,a; IV,A,2,a; IV,C,4,b

- Imidazo[1,2-*b*]-s-triazole: III,B,2,b; III,B,3,a; IV,A,1; IV,A,2,b;
IV,C,1,b; IV,C,4,b; IV,C,4,c; V,B; V,E; V,G,2
- Imidazo[1,5-*b*]-s-triazole: III,B,1,b; III,B,4,b; IV,A,1; IV,C,2; V,G
- Imidazo[2,1-*c*]-s-triazole: III,B,1,f; III,B,1,g; III,B,3,a; IV,C,1,b; V,B;
V,G,2
- Indolo[1,2-*b*]indazole: III,B,1,d
- Isoindolo[2,1-*a*]benzimidazole: III,B,1,b; III,B,1,f; III,B,4,a; III,B,5;
IV,A,1; IV,B,2; IV,C,2; IV,F; V,G,2; VI,C
- Isoindolo[1,2-*b*]benzothiazole: IV,C,4,b; IV,D,2
- Isoindolo[1,2-*b*]benzoxazole: IV,C,4,b
- Naphtho[1',2'-*d*]imidazo[3,2-*b*]thiazole: III,B,3,a
- Naphtho[1',2'-*d*]imidazo[2,1-*c*]-s-triazole: III,B,2,b; IV,A,2,b
- Oxazolo[3,2-*a*]benzimidazole: III,B,3,e
- Pyrazolo[1,5-*a*]benzimidazole: III,B,1,b; III,B,1,c; III,B,1,e; III,B,3,c;
IV,A,1; IV,C,2; IV,C,4,b; IV,D,2; IV,E; V,C; V,E; V,G,2;
VI,A; VI,B; VI,C
- Pyrazolo[5,1-*b*]benzothiazole: III,B,2,b; IV,C,4,b
- Pyrazolo[1,5-*a*]indole: III,B,1,d; III,B,1,f
- Pyrazolo[1,5-*d*]tetrazole: III,B,2,a; IV,A,1; IV,B,1; IV,C,2; V,A; V,B;
V,F; V,G,2
- Pyrazolo[5,1-*b*]thiazole: III,B,2,b; IV,C,4,b; VI,A
- Pyrazolo[3,2-*c*]-s-triazole: III,B,1,f; III,B,1,g; III,B,2,b; III,B,3,c;
IV,A,1; IV,C,4,b; IV,D,1; IV,D,2; V,B; V,C; V,E; V,G,2; VI,B
- Pyrazolo[1,5-*b*]-s-triazole: V,B
- Pyrazolo[1,5-*c*]-*v*-triazole: III,B,3,c
- Pyrrolo[1,2-*a*]benzimidazole: III,B,1,b; III,B,3,b; III,B,3,c; III,B,3,e;
III,B,4,a; IV,A,1; IV,A,2,a; IV,B,2; IV,C,1,a; IV,C,1,b; IV,C,2;
IV,C,4,b; IV,C,4,c; IV,D,2; V,B; V,F; V,G,2; V,H
- Pyrrolo[2,1-*b*]benzothiazole: III,B,3,c
- Pyrrolo[1,2-*a*]imidazole: II,C,1; II,C,2; III,B,3,b; III,B,3,c; III,B,4,a;
IV,A,1; IV,A,2,a; IV,B,2; IV,C,2; IV,C,4,b; IV,D,2; V,B; V,E;
V,F; V,G,2; VI,C
- Pyrrolo[1,2-*c*]imidazole: III,B,3,c
- Pyrrolo[1,2-*a*]indole: III,B,1,f; III,B,5; IV,C,2; VI,A
- Pyrrolo[2,1-*a*]isoindole: VI,A
- Pyrrolo[1,2-*b*]pyrazole: IV,A,1; IV,A,2,a; VI,A
- Pyrrolo[1,2-*a*]pyrrole (3a-azapentalene): II,C,1; III,B,5; IV,C,1,a; IV,F;
V,B; V,E; V,G,2; V,J; VI,A
- Pyrrolo[2,1-*b*]thiazole: II,C,1; III,B,3,b; III,B,3,c; IV,A,2,a; IV,C,1,a;
IV,C,4,b; IV,C,4,c; IV,D,1; IV,D,2; V,A; V,B; V,G,2; V,J
- Pyrrolo[1,2-*b*]-s-triazole: III,B,3,b; IV,C,4; V,B; V,E; V,G,2
- Pyrrolo[2,1-*c*]-s-triazole: III,B,3,b; V,B

- Pyrrolo[1,2-*c*]-*v*-triazole: III,B,4,b
Tetrazolo[1,5-*a*]benzimidazole: III,B,2,a; IV,B,1; V,G,2; VI,B
Tetrazolo[5,1-*b*]benzoselenazole: IV,B,1
Tetrazolo[5,1-*b*]benzothiazole: III,B,2,a; IV,B,1; IV,C,4,c; V,A; V,B;
V,C; V,E; V,F; V,G,2; VI,B; VII
Tetrazolo[5,1-*b*]benzoxazole: III,B,2,a; IV,B,1; VI,B
Tetrazolo[1,5-*b*]indazole: IV,B,1
Tetrazolo[5,1-*a*]isoindole: III,B,2,a; III,B,5; IV,A,1; IV,C,2
Tetrazolo[5,1-*b*]naphtho[1',2'-*d*]thiazole: III,B,2,a; V,F
Tetrazolo[5,1-*b*]naphtho[2',1'-*d*]thiazole: III,B,2,a; V,F
Tetrazolo[5,1-*d*]tetrazole: III,B,2,a; IV,B,1
[1,2,4]Thiadiazolo[2,3-*a*]benzimidazole: VI,A
[1,2,4]Thiadiazolo[4,5-*a*]benzimidazole: VI,A
[1,3,4]Thiadiazolo[3,2-*d*]tetrazole: III,B,3,d
Thiazolo[3,2-*a*]benzimidazole: III,B,1,f; III,B,2,b; III,B,3,a; IV,A,2,a;
IV,C,1,b; IV,C,2; V,B; V,E; V,G,2; V,H; VI,A; VI,B
Thiazolo[3,4-*a*]benzimidazole: III,B,1,b
Thiazolo[3,2-*d*]tetrazole: II,C,3; III,B,2,a; III,B,3,a; III,B,3,d; IV,B,1;
IV,C,4,b; IV,C,4,c; V,B; V,C; V,F; V,G,2; V,H
Thiazolo[3,2-*b*]-*s*-triazole: III,B,1,b; III,B,2,b; III,B,3,a; IV,A,2,a;
IV,C,4,b; V,E; V,F; V,G,2; V,H; VI,A
Thiazolo[2,3-*c*]-*s*-triazole: III,B,1,g; III,B,3,a; IV,A,2,b; IV,A,2,c; V,E;
V,F; V,G,2; V,H; VI,A
s-Triazolo[1,5-*a*]benzimidazole: III,B,2,b; IV,C,2; V,G,2
s-Triazolo[4,3-*a*]benzimidazole: III,B,2,b; IV,A,1; IV,A,2,b; IV,C,2;
V,C; V,E; V,G,2; VI,B
s-Triazolo[3,4-*b*]benzothiazole: III,B,1,e; III,B,1,g; III,B,2,b; IV,A,2,b;
IV,C,4,b; IV,C,4,c; IV,D,2; IV,E; V,B; V,C; V,E; V,G,2;
VI,A; VI,B
s-Triazolo[3,4-*b*]naphtho[2',1'-*d*]thiazole: III,B,2,b
s-Triazolo[3,4-*b*][1,3,4]oxadiazole: III,B,1,g; III,B,4,b; IV,E
s-Triazolo[2,3-*d*]tetrazole: III,B,2,a; III,B,3,d; IV,B,1
s-Triazolo[4,3-*d*]tetrazole: III,B,1,g; III,B,2,a; IV,C,2; V,G,2; V,H
s-Triazolo[3,4-*b*][1,3,4]thiadiazole: III,B,1,b; III,B,2,b; IV,A,2,b;
IV,A,2,c; IV,C,2; IV,E; V,A; V,B; V,C
s-Triazolo[4,3-*b*]-*s*-triazole: III,B,1,b; III,B,1,g; III,B,2,b; IV,A,1;
IV,A,2,b; IV,A,2,c; IV,C,2; IV,D,2; V,B; V,C; V,E; V,G,2
s-Triazolo[3,2-*c*]-*s*-triazole: III,B,1,a
s-Triazolo[3,4-*c*]-*s*-triazole: V,H
v-Triazolo[1,5-*a*]benzimidazole: III,B,1,c; IV,C,1,b
v-Triazolo[4,3-*b*]benzothiazole: III,B,1,c
v-Triazolo[4,3-*b*]benzoxazole: III,B,1,c

Azapentalenes of Type C

- Benzotriazolo[1,2-*a*]benzotriazole (dibenzo[*b, e*]-1,3a,6,6a-tetraazapentalene): III,C,1,a; III,C,2; IV,B,2; IV,C,2; IV,C,4,d; V,B; V,C; V,D; V,E; V,G,3; VI,C
- Benzotriazolo[2,1-*a*]benzotriazole (dibenzo[*b, f*]-1,3a,4,6a-tetraazapentalene): III,C,1,a; III,C,2; IV,B,2; IV,C,2; IV,C,4,d; IV,D,1; IV,E; V,A; V,B; V,C; V,D; V,E; V,G,3
- Indazolo[1,2-*a*]benzotriazole (dibenzo[*b, e*]-1,3a,6a-triazapentalene): III,C,1,a; IV,B,2; IV,C,1,a; IV,C,4,d; V,B; V,E
- Indazolo[2,1-*a*]benzotriazole (dibenzo[*b, f*]-1,3a,6a-triazapentalene): III,C,2
- Indazolo[2,1-*a*]indazole (dibenzo[*b, f*]-3a,6a-diazapentalene): IV,B,2
- Pyrazolo[1,2-*a*]benzotriazole (benzo[*b*]-1,3a,6a-triazapentalene): III,C,1,a; IV,B,2; IV,C,1,a; IV,C,4,d; V,G,3; VII
- Pyrazolo[1,2-*a*]indazole (benzo[*b*]-3a,6a-diazapentalene): V,A
- Pyrazolo[1,2-*a*]pyrazole (3a,6a-diazapentalene): III,C,1,b; IV,B,2; IV,C,1,a; IV,C,4,d; IV,D,2; V,B; V,E; V,F; V,G,3; VI,C; VII
- v*-Triazolo[1,2-*a*]benzotriazole (benzo[*b*]-1,3a,6,6a-tetraazapentalene): IV,B,2; IV,C,4,d; V,B; V,D; V,E
- v*-Triazolo[2,1-*a*]benzotriazole (benzo[*b*]-1,3a,4,6a-tetraazapentalene): III,C,1,a; IV,B,2; IV,C,2; IV,C,4,d; V,B; V,D; V,E; VI,C
- v*-Triazolo[2,1-*a*]-*v*-triazole (1,3a,4,6a-tetraazapentalene): II,C,1; III,C,2; IV,B,2; IV,C,4,d; IV,E; V,A; V,B; V,E

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Cyclazines and Related N-Bridged Annulenes

WILHELM FLITSCH AND ULF KRÄMER

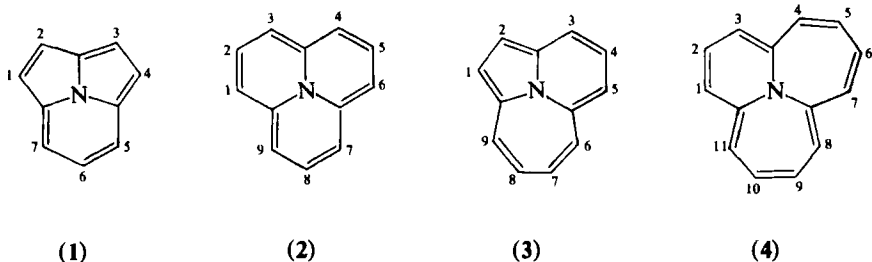
*Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität,
Münster, Germany*

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I. Introduction

Following a proposal of Boekelheide,^{1a,b} the word cyclazine is reserved to the general case of a conjugated, unsaturated cyclic molecule held planar by three covalent bonds to an internal nitrogen atom. The various possible cyclazines having rings of different size or different points of attachment to nitrogen can be distinguished by adding numbers in brackets, which indicate the number of atoms (on the ring) between the points of attachment to nitrogen, so **1** becomes cycl[3,2,2]azine; **2**, cycl[3,3,3]azine; **3**, cycl[4,3,2]azine; and **4**, cycl[4,4,3]azine. Numbering follows the IUPAC rules.^{1c}

Further substitution of the peripheral carbon atoms of the cyclazines by heteroatoms (N, S, etc.) is indicated in this chapter according to the "replacement nomenclature" system (aza, thia, etc.). Although, strictly, this runs contrary to the rules,^{1c} since it is a heterocyclic, not a hydrocarbon, system which is "replaced," the connection between closely related compounds can more clearly be seen. It should be noted that *Chemical Abstracts* employs the systematic fusion nomenclature; **1**, for instance, is pyrrolo[2,1,5-*cd*]indolizine.



The chemistry of cyclazines has not previously been reviewed. It is our aim to survey the methods of synthesis of these compounds and to show that the chemistry of cyclazines has stimulated discussion on theories of condensed π -systems. This latter point may be illustrated by an example: Early molecular orbital (MO) studies on cycl[3,3,3]azine (**2**) predicted a resonance energy greater than that for the highly stable

¹ (a) V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.* **80**, 2020 (1958); (b) R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *ibid.* **81**, 1459 (1959); (c) I.U.P.A.C.—Nomenclature of Organic Chemistry, Sections A, B, and C. Butterworths, London, 1969. See A. D. McNaught, *Adv. Heterocyclic Chem.* **20**, 176 (1976).

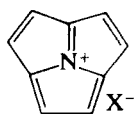
cycl[3,2,2]azine (1).¹⁻³ The complete lack of aromatic character⁴ was explained after the synthesis by improved theoretical treatments.^{5,6}

The present review includes hydrazino- and imino-bridged annulenes with internal nitrogen atoms coplanar with the peripheral atoms of the system. The literature is covered to the end of 1975, with some later references.

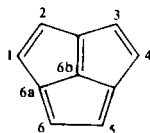
II. Cycl[2,2,2]azines

Cycl[2,2,2]azinium salts⁷ (5) have not been reported so far. Hückel molecular orbital (HMO)-calculations of the isoelectronic acepentylene (6) lead to two singly occupied degenerate HOMO's.^{8,9} Since there is no contribution in both the HOMO's and the LUMO from atom 6b this situation does not change in going from 6 to the 5-ion,¹⁰ which can be represented as an annulene derivative of the $(4n + 1)$ π -type.

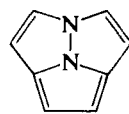
HMO-treatment reveals a closed-shell system for the dianion of 6, thus indicating stabilization for isoelectronic cycl[2,2,2]azines with an additional nitrogen atom in a peripheral position, e.g., 7. Compounds of this type can be prepared by cycloaddition reactions.



(5)



(6)



(7)

When 1-benzoyl-2-phenyl-4,8-diazapentalene (8) was treated with dimethyl acetylenedicarboxylate under dehydrogenating conditions, 1-phenyl-2-benzoyl-5,6-dicarbomethoxy-2a-azacycl[2,2,2]azine (9a) was

² R. D. Brown and B. A. W. Collier, *Mol. Phys.* **2**, 158 (1959).

³ A. Streitwieser, "Molecular Orbital Theory for Organic Chemists." Wiley, New York, 1961.

⁴ D. Farquhar and D. Leaver, *Chem. Commun.*, **24** (1969); D. Farquhar, T. T. Gough, and D. Leaver, *J. Chem. Soc., Perkin Trans. I*, 341 (1976).

⁵ B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron* **28**, 3657 (1972).

⁶ M. J. S. Dewar and N. Trinajstić, *J. Chem. Soc. A*, 1754 (1969).

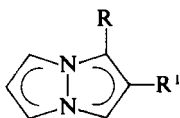
⁷ Cyclazinium salts with an odd number of peripheral carbon atoms do not rank among the class of cyclazines in the narrow sense.

⁸ HOMO = highest occupied MO; LUMO = lowest unoccupied MO.

⁹ R. Zahradnik and J. Michl, *Collect. Czech. Chem. Commun.* **30**, 3529 (1965).

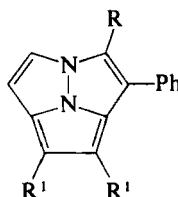
¹⁰ (a) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry." McGraw-Hill, New York, 1969; (b) E. Heilbronner and H. Bock, "Das HMO-Modell und seine Anwendung." Verlag Chemie, Weinheim, 1968.

formed. Hydrolysis gave the corresponding acid (**9b**), which on heating underwent decarboxylation to give **9c**. Treatment of **9c** with potassium hydroxide in ethanol gave in high yield **9d**.¹¹ The compounds **9** are diatropic, confirming the closed-shell arrangement of the π -electrons.



(8)

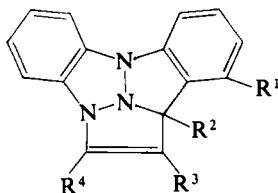
R = CPh; R¹ = Ph



(9)

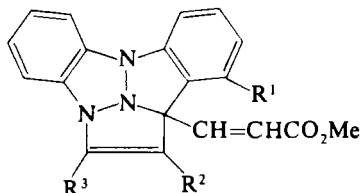
	R	R¹
a:	CPh	CO ₂ Me
b:	CPh	COOH
c:	CPh	H
d:	H	H

Cycloaddition reactions of mesoionic di- and triazapentalenes have been reported recently: 1:1-adducts (**10**)¹² and 1:2-adducts of proved (**11**)¹² and assumed (**12**)¹³ and **13**)¹² structure have been described. These compounds will not be discussed in detail since they do not contain fully conjugated perimeters.¹⁴ Dehydrogenation of **10**, **12**, or **13** has not yet been attempted.



(10)

R¹, R² = H, Me
R³, R⁴ = H, Me, Ph, CO₂Me



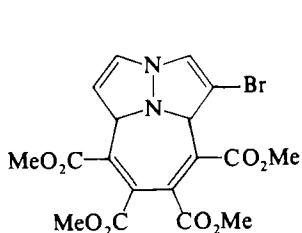
(11)

¹¹ V. Boekelheide and N. A. Fedoruk, *Proc. Natl. Acad. Sci. U.S.A.* **55**, 1385 (1966); **65**, 13683 (1966).

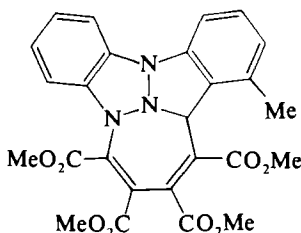
¹² O. Tsuge and H. Samura, *Tetrahedron Lett.*, 597 (1973); *Heterocycles* **2**, 27 (1974).

¹³ W. Flitsch and S. R. Schindler, unpublished results.

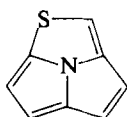
¹⁴ For similar reactions of dimethyl acetylenedicarboxylate and thiazolo[3,4-*b*]-indazole, see K. T. Potts and J. L. Marshall, *J. Org. Chem.* **41**, 129 (1976).



(12)



(13)



(14)

Attempts to synthesize thiacycl[2,2,2]azines (14) failed.¹⁵

III. Cycl[3,2,2]azines

Cycl[3,2,2]azines (1) are stable aromatic compounds that have been investigated extensively (Table I).

A. SYNTHESIS

Most of the methods of forming cycl[3,2,2]azine derivatives involve indolizines. Other precursors are 3*H*-pyrrolizines and pyridines.

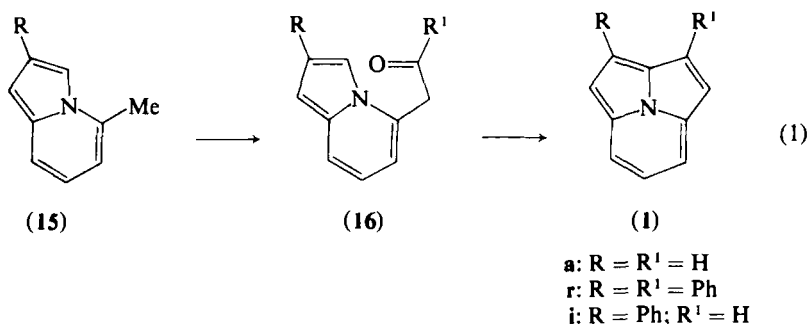
1. Intramolecular Condensation of Indolizines

The methyl group in 5-methylindolizines is sufficiently active to allow the introduction of functional groups. Indolizines (15) with *n*-butyllithium followed by *N,N*-dimethylamides give, after hydrolysis, ketones 16. Cyclodehydration to 1 takes place in glacial acetic acid [Eq. (1)]; more severe conditions, such as in hydrogen fluoride, were ineffective, presumably owing to protonation of the indolizine nucleus.¹

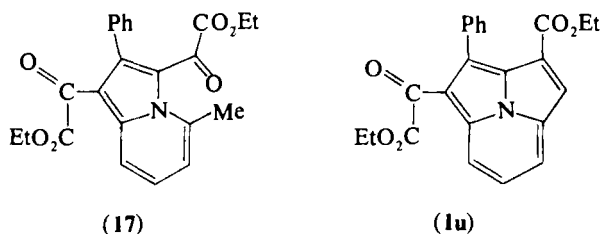
¹⁵ O. Ceder and B. Beijer, *Tetrahedron* **28**, 4341 (1972).

TABLE I
CYCL[3,2,2]AZINES (I) DISCUSSED IN THIS SECTION

No.	1	2	3	4	5	6	7	References
1a	H	H	H	H	H	H	H	1b, 23, 32
1b	D							53
1c	Me							39
1d	CO ₂ Me							43, 56
1e	COMe							1b, 43
1f	COPh							43
1g	NO ₂							1b
1h		Me						39
1i		Ph						1b, 23
1j						NO ₂		32
1k	COOH	COOH						23
1l	CO ₂ Me	CO ₂ Me						23, 39
1m	COMe		Me					43
1n	COPh		Me					43
1o	D			D				49, 50
1p	Br			Br				1b
1q	COMe			COMe				1b
1r		Ph	Ph					1b
1s		CO ₂ Me	Ph					57
1t					CO ₂ Me	CO ₂ Me		32
1u	COCO ₂ Et	Ph	CO ₂ Et					16
1v	CH ₂ CO ₂ Me	CO ₂ Me		CO ₂ Me				39, 40
1w	CH(CO ₂ Et) ₂	CO ₂ Me		CO ₂ Me				40
1x			Cl		CO ₂ Me	CO ₂ Me		33
1y					CO ₂ Me	CO ₂ Me	CO ₂ Et	38
1z	CONH ₂	SMe	CO ₂ Me	CO ₂ Me				42

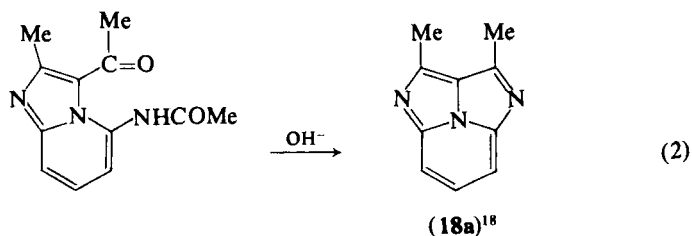


5-Methyl-2-phenylindolizine reacts with ethoxalyl chloride to give the 1,3-diethoxalyl derivative (17). Heating in ethanolic sodium ethoxide converts 17 partly into cycl[3,2,2]azine (1u) and partly into the salt of a hydroxycycl[3,3,2]azinone (45a) (Section IV).¹⁶



This method of synthesis is not general since a carbonyl substituent at the 3-position of indolizines is usually deactivated toward nucleophilic attack.^{17, 18}

The synthesis of 1,4-diazacycl[3,2,2]azines (18) has been carried out as shown in Eqs. (2) and (3).^{18, 19}

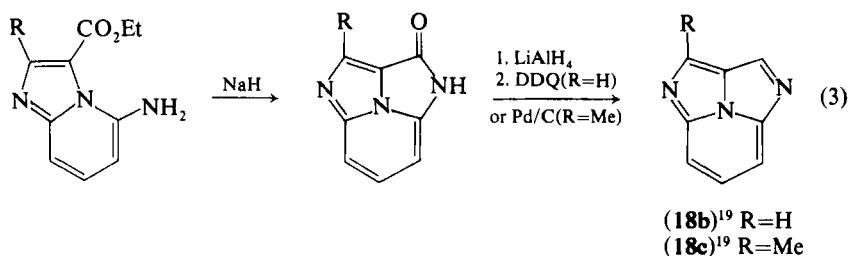


¹⁶ W. K. Gibson, D. Leaver, J. E. Roff, and C. W. Cummings, *Chem. Commun.*, 214 (1967).

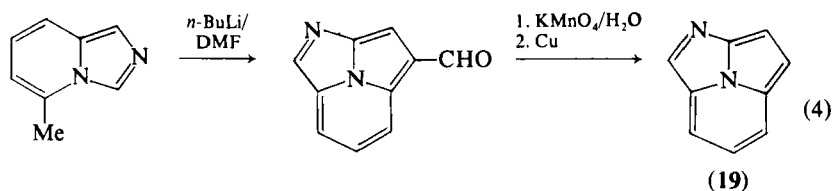
¹⁷ W. Flitsch and E. Gerstmann, *Chem. Ber.* **105**, 2344 (1972).

¹⁸ K. Valentin and A. Taurins, *Tetrahedron Lett.*, 3621 (1966).

¹⁹ W. W. Paudler, R. A. VanDahm, and Y. N. Park, *J. Heterocycl. Chem.* **9**, 81 (1972).



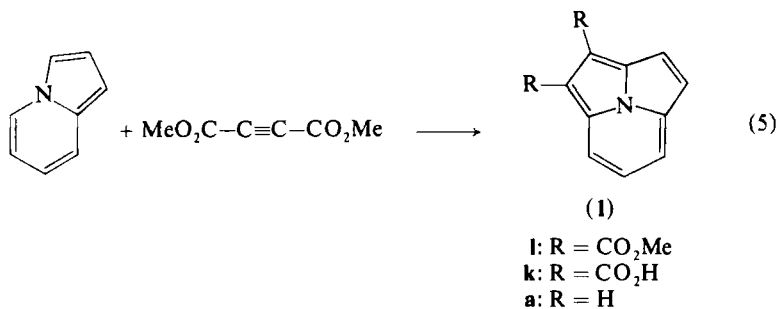
The reaction of 2,6-diaminopyridine with bromomalondialdehyde does not result in the formation of **18b**, yielding instead 5-amino-2-formylimidazo[1,2-*a*]pyridine.²⁰



2-Azacycl[3,2,2]azine (**19**) has been prepared by the reaction sequence given in Eq. (4).²¹

2. Cycloaddition to Indolizines

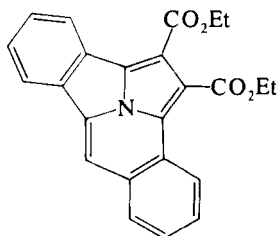
The reaction of indolizines with dialkyl acetylenedicarboxylates in the presence of a dehydrogenating catalyst leads to 1,2-dicarboxycycl[3,2,2]azines.^{22,23} Methyl phenylpropiolate may be used instead, although attempts to effect reaction between indolizine and certain other dienophiles including diphenylacetylene, diethyl azodicarboxylate, and 1,3-cyclohexadiene were unsuccessful. Hydrolysis of the diesters yielded the corresponding acids. Subsequent decarboxylation proceeded in high yield using copper chromite in quinoline [Eq. (5)].



²⁰ O. Ceder, K. Rosén, and J. F. Witte, *Acta Chem. Scand.* **27**, 1817 (1973).

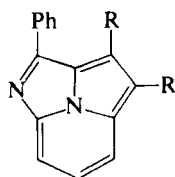
²¹ O. Fuentes and W. W. Paudler, *J. Org. Chem.* **40**, 1210 (1975).

²² J. C. Godfrey, *J. Org. Chem.* **24**, 581 (1959).



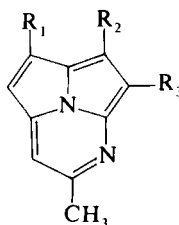
(20)

The first cycl[3,2,2]azine derivative prepared in this way was **20**.²² Theoretical considerations concerning the mechanism of the reaction have been presented.^{23b} 1-Azacycl[3,2,2]azines (**21**)²⁴ and 5-azacycl[3,2,2]azines (**22a**)²⁵ may be obtained by the same route. 5-Azacycl[3,2,2]azines (**22b**)²⁶ have been obtained recently by Vilsmeier reaction of the corresponding 5,7-dimethyl-6-azaindolizines.



(21)

R = CO₂Me, CO₂H, H



(22)

a: R₁ = Ph; R₂ = R₃ = CO₂Me, CO₂H, H
b: R₁ = CH₃, Ph; R₂ = H; R₃ = CHO

The reaction of 5-azaindolizines with dimethyl acetylenedicarboxylate gave the compounds **23** and **24**. Attempts to remove a hydride ion from the dihydro-4a-azacycl[3,2,2]azines (**24**) failed.²⁷

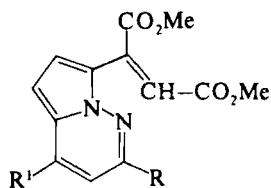
²³ (a) A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.* **24**, 582 (1959); (b) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.* **83**, 453 (1961); (c) V. Boekelheide and K. Fahrenholtz, *ibid.* **83**, 458 (1961).

²⁴ V. Boekelheide and A. Miller, *J. Org. Chem.* **26**, 431 (1961).

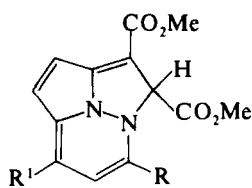
²⁵ V. Boekelheide and S. S. Kertelj, *J. Org. Chem.* **28**, 3212 (1963).

²⁶ R. Buchan, M. Fraser, and C. Shand, *J. Org. Chem.* **41**, 351 (1976).

²⁷ W. Flitsch and U. Krämer, *Tetrahedron Lett.*, 1479 (1968); *Justus Liebigs Ann. Chem.* **735**, 35 (1970); M. Zupan, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **8**, 1 (1971).



(23)



(24)

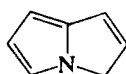
R = R' = H, Me, Ph
R = Me; R' = Ph

3. Cycloaddition to Methylenepyrrolizines

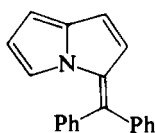
Methylenepyrrolizines are important precursors in the synthesis of cycl[3,2,2]azine derivatives. They may be obtained in three different ways.

i. Compounds **26**^{28,29} and **27**³⁰ have been prepared by condensation of 3*H*-pyrrolizine (**25**)³¹ with the corresponding ketones.

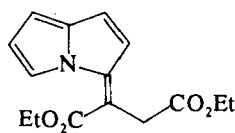
ii. Vilsmeier reaction of **25** gave the salt **28a**, which was converted by treatment with dimethylthioformamide and acetic anhydride³² into a mixture of isomers containing the bismethylenepyrrolizine derivative (**29a**). 2,3-Dihydro-1*H*-pyrrolizin-1-one (**30**) was treated with the Vilsmeier complex at -40° to give the perchlorate (**28b**) in good yield, the trisubstituted derivative (**31**) being the sole product isolated from a reaction at 0° . A disubstituted Vilsmeier salt (**29b**) was obtained from **28b** with dimethylthioformamide.³³



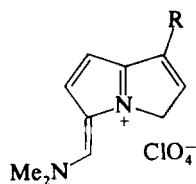
(25)



(26)



(27)



(28)

a: R = H
b: R = Cl

²⁸ W. H. Okamura and T. J. Katz, *Tetrahedron* **23**, 2941 (1967).

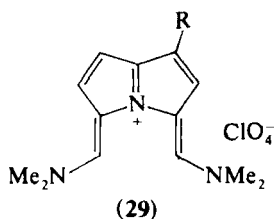
²⁹ W. Flitsch and R. Heidhues, *Chem. Ber.* **101**, 3843 (1968).

³⁰ D. Johnson and G. Jones, *J. Chem. Soc., Perkins Trans. 1*, 840 (1972).

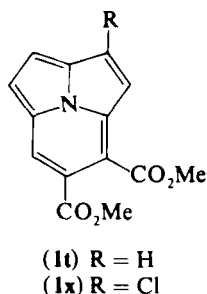
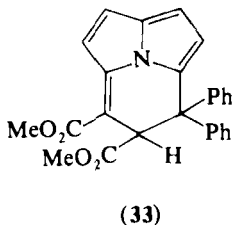
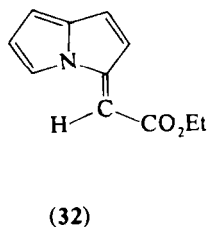
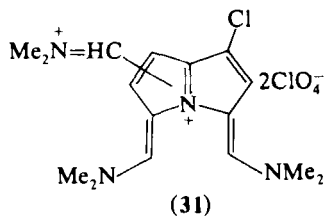
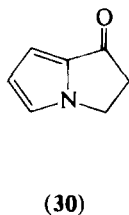
³¹ E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.* **86**, 2963 (1964).

³² M. A. Jessep and D. Leaver, *J. Chem. Soc., Chem. Commun.*, 790 (1970).

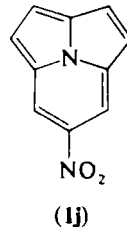
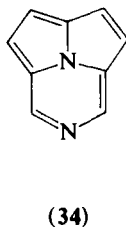
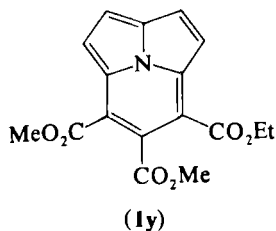
³³ W. Flitsch and J. Koszinowski, unpublished results.



a: R = H
b: R = Cl



iii. Reactions of methylene-3*H*-pyrrolizine derivatives with acetylenedicarboxylates offer attractive routes to cycl[3,2,2]azines. The diphenyl derivatives (26) readily gave the cycl[3,2,2]azine derivative (33). In contrast compound 27 proved to be inert toward dienophiles.³⁰



The conjugate bases of 28 are unstable, but treatment of the salts with sodium hydride in the presence of dimethyl acetylenedicarboxylate gave the cycl[3,2,2]azine derivatives 1t³² and 1x.³³

3-Ethoxycarbonylmethylene-3*H*-pyrrolizine (32), prepared from pyrrolizin-3-one with ethoxycarbonylmethylenetriphenylphosphorane,³⁴⁻³⁶ reacted slowly with dimethyl acetylenedicarboxylate to give a mixture of products from which the [3,2,2]azine 1y was isolated in 12%¹yield.³⁷

³⁴ W. Flitsch and U. Neumann, *Chem. Ber.* **104**, 2170 (1971).

³⁵ U. Neumann, Dissertation, Münster 1973.

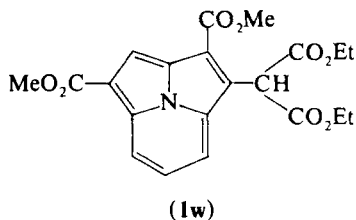
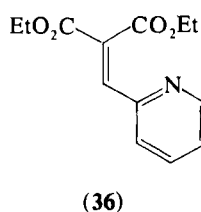
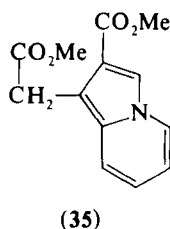
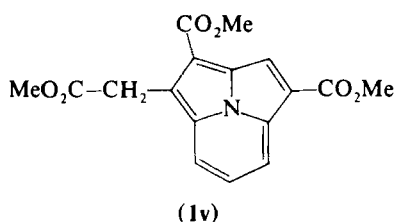
³⁶ W. Flitsch and S. R. Schindler, *Synthesis*, 685 (1975).

³⁷ D. Johnson and G. Jones, *J. Chem. Soc., Perkin Trans. 1*, 2517 (1972).

6-Azacycl[3,2,2]azines (**34**)³⁸ and 6-nitrocycl[3,2,2]azine (**1j**) were obtained from **29** by treatment with ammonia and nitromethane, respectively.^{32,33}

4. Cycloaddition to Pyridines

The cyclazine (**1v**) was the only product isolated in poor yield from reaction of pyridine and methyl propiolate in acetonitrile. The indolizine derivative (**35**) may be an intermediate, since it was obtained from a similar reaction in ether.³⁹ 2-Acetylpyridine and ethyl pyridine-2-carboxylate reacted similarly.⁴⁰



Better yields may be obtained from vinylpyridines and alkyl propiolates, as can be seen from the conversion of **36** to the cycl[3,2,2]-azine (**1w**).⁴¹ Reaction of α -(bismethylthio)methylene-2-pyridineacetonitrile and ethyl bromoacetate using triethylamine afforded the indolizine derivative (**37**). Dimethyl 1-carbamoyl-2-methylthiocycl[3,2,2]azine-3,4-dicarboxylate (**1z**) was synthesized by allowing dimethyl acetylenedicarboxylate to react with indolizine derivative **38**, which was obtained by decarboxylation of **37** using sulfuric acid in presence of palladium-on-charcoal as catalyst [Eq. (6)].⁴²

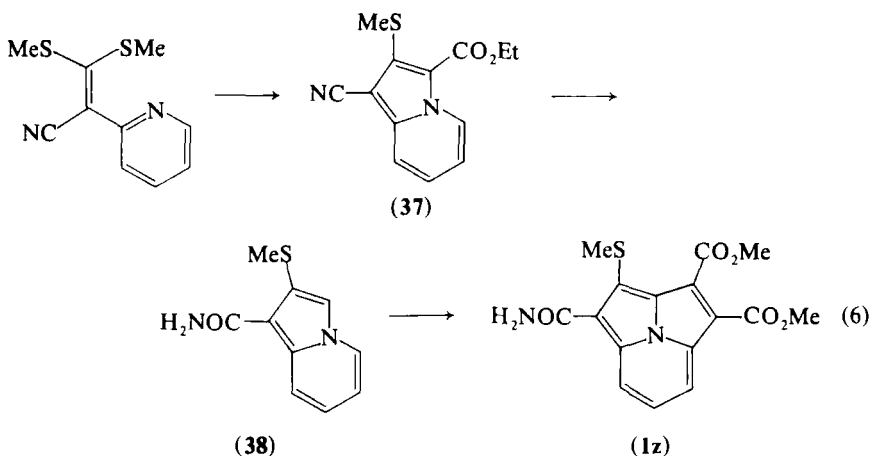
³⁸ Compound **34** has been obtained from 7-azaindolizine by treatment with dialkyl acetylenedicarboxylates and subsequent hydrolysis and decarboxylation (K. Untch, personal communication).

³⁹ R. M. Acheson and D. A. Robinson, *J. Chem. Soc., Chem. Commun.*, 175 (1967); R. M. Acheson and D. A. Robinson, *J. Chem. Soc. C*, 1633 (1968).

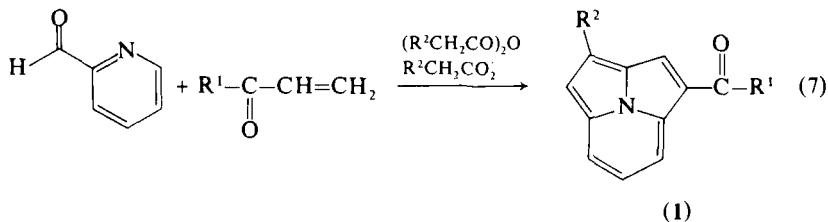
⁴⁰ R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 740 (1975).

⁴¹ R. M. Acheson and J. Woollard, *J. Chem. Soc. C*, 3296 (1971).

⁴² C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Heterocycles* **2**, 264 (1974).



Acylative cyclization of the readily available 2-pyridinecarbaldehyde with an α,β -unsaturated carbonyl compound provides a new and convenient route to 1-acylcycl[3,2,2]azines [Eq. (7)]. A mechanism for this interesting reaction has been suggested.⁴³



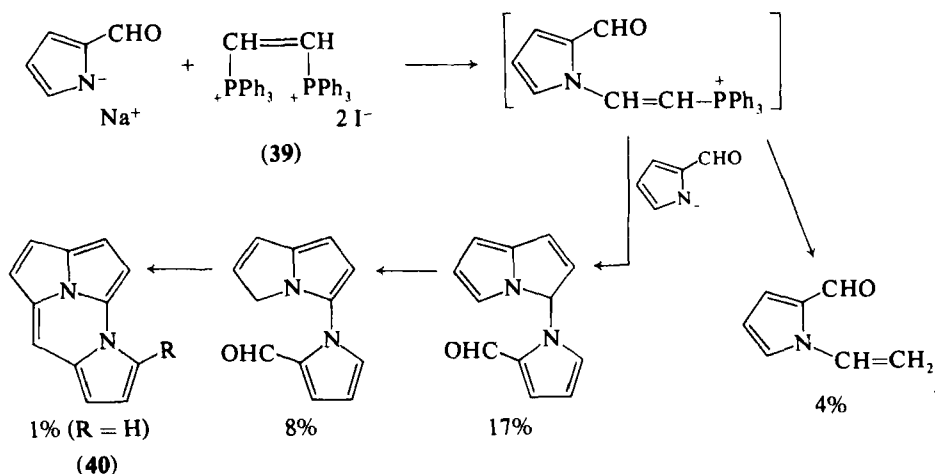
	R ¹	R ²	%
e:	Me	H	60–70
m:	Me	Me	~50
f:	Ph	H	~40
n:	Ph	Me	~20
d:	OMe	H	~15

5. Other Methods

Pyrrolo[1',2'-3,4]pyrimido[2,1,6-*cd*]pyrrolizine (**40a**) was obtained in 10% yield by a reaction of the sodium salt of pyrrole-2-aldehyde with vinylene-1,2-bis(triphenyl)phosphonium iodide (**39**) in boiling toluene. The intermediate (yields shown in Scheme 1) were isolated from a reaction in boiling benzene. Compound **40a** is diatropic and on refluxing in acetic anhydride it gives **40b**. The position of substitution is in accordance with HMO calculations.⁴⁴

⁴³ E. Pohjala, *Acta Chem. Scand., Ser. B*, **28**, 582 (1974); *Heterocycles* **2**, 585 (1974).

⁴⁴ W. Flitsch and E. R. Gesing, *Tetrahedron Lett.*, 1997 (1976).

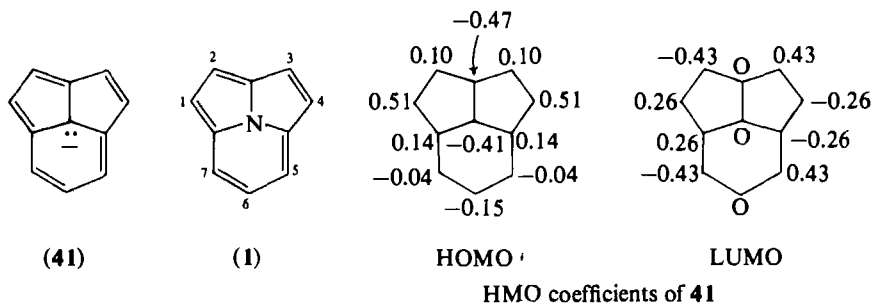


a: R = H
b: R = COMe

SCHEME 1

B. PHYSICOCHEMICAL PROPERTIES

Cycl[3,2,2]azine (**1**) is related to annulenes as well as to nonalternant hydrocarbons;⁴⁵ that is, it can be considered as an amino-substituted [10] annulene and at the same time as isoelectronic with the aceindenyl anion (**41**).⁴⁶



According to MO calculations, **41** is a closed-shell molecule, the maximum π -electron density being at the central carbon atom.^{9,47} Thus aza substitution to cycl[3,2,2]azine (**1**) gives considerable stabilization.

⁴⁵ F. Gerson, *Pure Appl. Chem.* **28**, 148 (1971).

⁴⁶ Compound **41** was prepared recently: P. Eilbracht and K. Hafner, *Angew. Chem.* **83**, 802 (1971); *Angew. Chem., Int. Ed. Engl.* **10**, 751 (1971).

⁴⁷ P. Hochmann, R. Zahradnik, and V. Kvasnička, *Collect. Czech. Chem. Commun.* **33**, 3478 (1968).

The HMO resonance energy per electron (REPE value^{5,48}) using an appropriate reference structure was found to be 0.040β (cf. pyrrole 0.039β , indolizine 0.027β).⁵

According to PMO theory¹⁰ the introduction of a central nitrogen into the aceindenyl anion (**41**) leaves the energy of the LUMO unchanged, but lowers that of the HOMO. The introduction of nitrogen atoms into the perimeter also affects the HOMO–LUMO separation. Enhancement of the electronegativity in positions 1, 4^{18,19,24} and 6^{32,33} increases this energy difference.

Cycl[3,2,2]azines are diatropic. The proton magnetic resonance (PMR) spectrum of the parent compound (**1a**) consists of an A₂B multiplet from the protons of the six-membered ring and one AB quartet from the two pairs of protons of the five-membered rings.

The assignment of the higher-field doublet of the AB spectrum to the 1- and 4-protons was based on the observation that this absorption was absent in the spectrum of dideutero[3,2,2]cyclazine (**1o**) prepared by acid-catalyzed hydrogen–deuterium exchange. It was predicted on the basis of HMO localization energies that exchange would occur at the 1- and 4-positions.⁴⁹ These spectral assignments have been confirmed by additional arguments⁵⁰ and are in agreement with the results from substituted cyclazines (Table II).

A comparison of the PMR spectra of cycl[3,2,2]azine (**1a**) and 2-azacycl[3,2,2]azine (**19**) reveals a deshielding of 1.26 ppm brought about by the anisotropic contribution of the peripheral nitrogen to the proton of the adjacent carbon atom. The peri interaction to the proton in position 3 gives rise to a deshielding of 0.15 ppm. A localization of the C3–C4 double bond is deduced from CNDO/2 (complete neglect of differential overlap) calculations. Some experimental verification for this is found in the size of $J_{3,4} = 4.7$ Hz, suggesting a π -bond order of 0.8.²¹ The PMR spectra of 3-phenylcycl[3,2,2]azines have been studied using the shift reagent Eu(fod)₃.⁵¹

The first four absorption bands of the *UV spectrum* of cycl[3,2,2]azine (**1a**) have been assigned from theoretical predictions based on MO models together with the experimental polarization

⁴⁸ For a review of various definitions of aromaticity and their application in heterocyclic chemistry, see M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.* **17**, 255 (1974).

⁴⁹ V. Boekelheide, F. Gerson, G. Heilbronner, and D. Meuche, *Helv. Chim. Acta* **46**, 1951 (1963).

⁵⁰ L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Aust. J. Chem.* **18**, 1221 (1965).

⁵¹ C. M. Gupta, B. B. P. Srivastava, R. K. Rizvi, and N. Anand, *Ind. J. Chem.* **12**, 674 (1974).

TABLE II
PROTON MAGNETIC RESONANCE SPECTRA OF CYCL[3,2,2]AZINES (δ -VALUES, TMS STANDARD)

No.		1-H	2-H	3-H	4-H	5-H	6-H	7-H	J (Hz)	Solvent	References
1a	—	7.19	7.50	7.50	7.19	7.86	7.86(?)	7.86	$J_{12} = 4.2; J_{56} = 8.0$	CDCl ₃	21
		7.20	7.51	7.51	7.20	7.86	7.59	7.86	$J_{12} = 4.2; J_{56} = 8.0$	CCl ₄	49
1c	1-Me	(2.73)	7.32	7.47	7.15	7.88	7.57	7.83	$J_{34} = 4.3; J_{56} = 8.0$	CCl ₄	39
1h	2-Me	6.93	(2.74)	7.47	7.11	7.69	7.51	7.69		CCl ₄	50
1i	1-CO ₂ Me	—	—	7.63	7.25	7.84	7.69	8.30		CCl ₄	50
	2-CO ₂ Me										
1j	6-NO ₂	7.55	7.75	7.75	7.55	8.86	—	8.86	$J_{12} = 4.5$	CDCl ₃	32
19	2-Aza-	8.45	—	7.65	7.30	7.96	7.51	7.82	$J_{14} = 1.0; J_{34} = 4.7; J_{56} = 7.8; J_{67} = 7.0$	CDCl ₃	21
34	6-Aza-	7.44	7.64	7.64	7.44	9.21	—	9.21	$J_{12} = 4.5$	CDCl ₃	32
18b	1,4-Diaza	—	8.70	8.70	—	8.12	8.12	8.12	$J_{56} = 8.0^a$	CDCl ₃	19, 21
18a	2,3-Di-Me- 1,4-diaza	—	(2.92)	(2.92)	—	7.78	8.00	7.78	$J_{56} = 8.0$	CDCl ₃	18, 19

^a Eurosolve.

directions. The UV spectrum of the conjugate acid of **1a** ($pK = -2.8$ on a Hammett H_0 -scale) confirms that protonation occurs in position 1.⁵²

The *ESR spectra* of the radical anions of cycl[3,2,2]azine (**1a**),⁵³ 1,4-dideuteriocycl[3,2,2]azine (**1o**),⁵³ 6-nitrocycl[3,2,2]azine (**1j**)⁵⁴ and 6-azacycl[3,2,2]azine (**34**)⁵⁴ have been described and discussed in terms of simple MO theory.

A determination of the *structure* of 1,4-dibromocycl[3,2,2]azine (**1p**) was complicated by the considerable anisotropy of thermal motion of the bromine atoms. It was concluded that the nitrogen configuration is probably planar, but, if not, the nitrogen atom is less than 0.07 Å out of the mean plane of the molecule.⁵⁵

C. CHEMICAL PROPERTIES

In terms of chemical reactivity, cycl[3,2,2]azine shows the normal behavior of a stable aromatic system, undergoing substitution reactions smoothly and in good yields. From MO calculations it was predicted that electrophilic substitution should occur most readily at the 1-position.^{1b} Reaction at positions 2, 5, and 6 have not yet been observed.

Diacetylation of 2,3-diphenylcycl[3,2,2]azine (**1r**) takes place in positions 1 and 4, indicating that the heterocyclic system is more prone to electrophilic attack than the phenyl groups.^{1b}

A mixture of 79% 1,4-dideuteriocycl[3,2,2]azine (**1o**), 19% 1-deuteriocycl[3,2,2]azine (**1b**) and 2% unchanged **1a** was obtained by treating **1a** with deuteriosulfuric acid. The structure of **1o** follows from the PMR spectrum and additional theoretical considerations.⁴⁹ The site of protonation of 2-azacycl[3,2,2]azine (**19**) has been shown to be N-2 rather than C-3 by PMR spectroscopy.²¹

Nitration, bromination and acetylation of cycl[3,2,2]azine (**1a**) have been realized (Scheme 2), but attempts to obtain azo coupling products failed.^{1b}

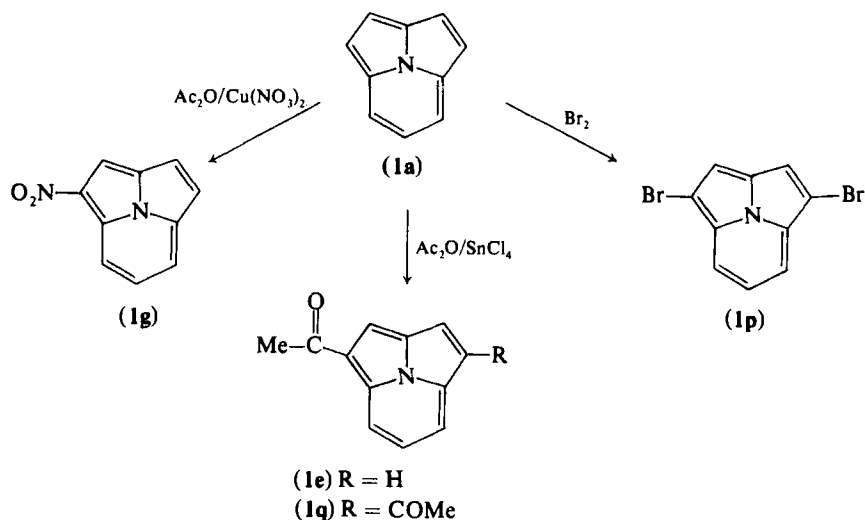
Diacetylation occurred even though unchanged **1a** was recovered, suggesting that the rate of introduction of the second acetyl group is not appreciably decreased by the presence of the first. Similarly, no monobromo derivative could be isolated in the bromination reaction.

⁵² F. Gerson, E. Heilbronner, N. Joop, and H. Zimmermann, *Helv. Chim. Acta* **46**, 1940 (1963).

⁵³ F. Gerson and J. H. Hammons, in "Nonbenzenoid Aromatics" (J. P. Snyder, ed.), Vol. II, pp. 137-139. Academic Press, New York, 1971.

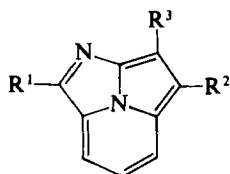
⁵⁴ F. Gerson, J. Jachimowicz, D. Kowert, and D. Leaver, *Helv. Chim. Acta* **56**, 258 (1973).

⁵⁵ A. W. Hanson, *Acta Crystallogr.* **14**, 124 (1961).



SCHEME 2

The monosubstitution products of the Friedel–Crafts reaction and of the nitration reaction have been interrelated to show that the substituent group is introduced at the same position in each case. A further correlation with the adduct (1d) from indolizine and methyl propiolate provides evidence that this is the 1-position as predicted.⁵⁶ Acylation of 2-methoxycarbonyl-3-phenylcyclo[3,2,2]azine (1s) takes place in the pyrrole part of the molecule.⁵⁷



(19)

- a:** $R^1 = R^2 = R^3 = H$
b: $R^1 = Br; R^2 = R^3 = H$
c: $R^1 = R^2 = Br; R^3 = H$
d: $R^1 = R^2 = R^3 = Br$
e: $R^1 = R^3 = H; R^2 = NO_2$
f: $R^1 = R^2 = NO_2; R^3 = H$
g: $R^1 = CHO; R^2 = R^3 = H$
h: $R^2 = CHO; R^1 = R^3 = H$
i: $R^1 = C_4H_9; R^2 = R^3 = H$

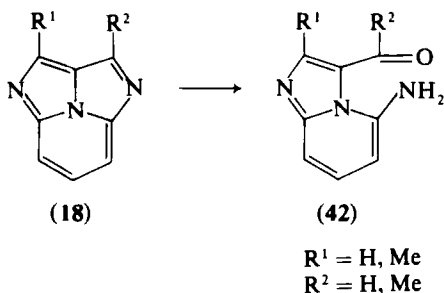
⁵⁶ V. Boekelheide and T. Small, *J. Am. Chem. Soc.* **83**, 462 (1961).

⁵⁷ C. M. Gupta and N. Anand, *Ind. J. Chem.* **11**, 427 (1973).

Bromination of 2-azacycl[3,2,2]azine (**19a**) under different conditions afforded compounds **19b–19d**. Nitration yielded **19e** and **19f**; Vilsmeier formylation, the aldehydes **19g** and **19h**.⁵⁸

Compound **19a** reacts with butyllithium to form the 1-butyl derivative (**19i**). Nucleophilic displacement reactions of polyhalogenated 2-azacycl[3,2,2]azine derivatives have been investigated.⁵⁹ Considering the eigenvector pattern of the LUMO of the aceindenyl anion (Section III,B), one can easily deduce that the introduction of a nitrogen atom in position 2 (and 4) should lower the orbital energy, thus raising the electrophilicity of the compound. This may explain the facile acid-catalyzed hydrolyses of 1,4-diazacycl[3,2,2]azines (**18**) affording substituted imidazo[1,2-*a*]pyridines (**42**).¹⁹

The UV spectrum of protonated 2-phenyl-1-azacycl[3,2,2]azine (**21**) resembles that of the conjugate base²⁴ whereas there is a large difference between the UV spectra of the protonated and the unprotonated 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (**22**).²⁵ The arguments given above suggest that this anomaly is caused by hydrolysis of **22**.



IV. Cycl[3,3,2]azines

Cycl[3,3,2]azinium salts **43**, which should be potentially capable of being aromatic,^{1b} have hitherto not been available for study.^{59a}

The base peak of the mass spectrum of 1-methylcycl[3,2,2]azine (**1c**) was proposed to be due to the cation (**43**) being formed by ring expansion.³⁹

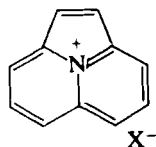
The "second stable adduct"⁶⁰ of 2-styrylpyridine and dimethyl acetylenedicarboxylate was shown to be 2a,3,4,5-tetramethoxy-

⁵⁸ O. Fuentes and W. W. Paudler, *J. Org. Chem.* **40**, 3065 (1975).

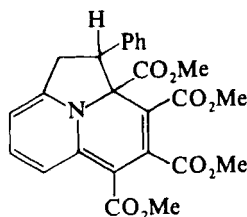
⁵⁹ O. Fuentes and W. W. Paudler, *J. Heterocycl. Chem.* **12**, 925 (1975).

^{59a} Note added in proof: recently salts (**43**) have been obtained on two independent routes. D. Leaver, private communication.

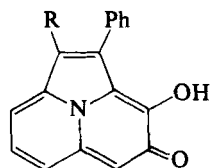
⁶⁰ O. Diels and F. Möller, *Justus Liebigs Ann. Chem.* **516**, 45 (1935).



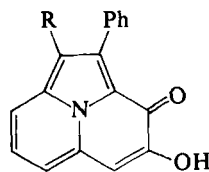
(43)



(44)

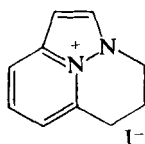


or

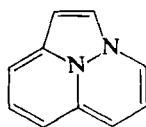
(45) a: R = COCO₂Et
b: R = H

carbonyl-2-phenyl-1,2-dihydrocyclo[3,3,2]azine (44).⁶¹ The cyclo[3,3,2]-azine derivative **45a**, which is related to 3*H*-cyclo[3,3,2]azine as tropolone is to cycloheptatriene, has been obtained as a minor product in the reaction of diethoxalyl indolizine (17) with sodium ethoxide (Section III,A,1). Standard procedures converted **45a** into the hydroxyphenylcyclo[3,3,2]azinone (**45b**). The PMR spectrum of **45b** showed signals for ring protons in the region $\delta = 7.2\text{--}8.2$ ppm (in CDCl₃).¹⁶

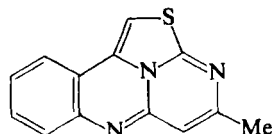
Derivatives containing a pyrrole or thiophene-type heteroatom in the periphery may be looked at only formally as cyclo[3,3,2]azines since they are isoelectronic with the cyclo[3,3,3]azines described in Section V. 4,5-Dihydro-3*H*-2a-azacyclo[3,3,2]azinium iodide (**46**) has been prepared, but could not be converted into 2a-azacyclo[3,3,2]azine (**47**).⁶²



(46)



(47)



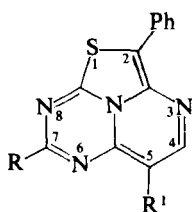
(48)

Attempts to synthesize quinolino[4,3-*d*]thiazoles resulted in the formation of the 2,3,6-thiadiazabenzocyclo[3,3,2]azine (**48**).⁶³

⁶¹ R. M. Acheson and R. S. Feinberg, *Chem. Commun.*, 342 (1965).

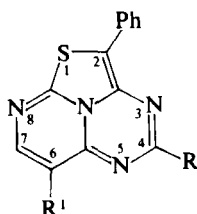
⁶² V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.* **33**, 2062 (1968).

⁶³ G. deStevens and V. P. Arya, *J. Org. Chem.* **29**, 2064 (1964).



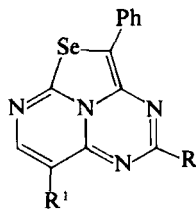
(49)

R = H, Me
R¹ = H, CO₂Et



(50a)

R = Me
R¹ = H, CO₂Et



(50b)

R = H, Me
R¹ = H, CO₂Et, Br

The thiatriazacycl[3,3,2]azine derivatives **49** and **50a**⁶⁴ and selenatriazacycl[3,3,2]azines (**50b**)⁶⁵ have been prepared in a way closely related to the synthesis of polyazacycl[3,3,3]azines described in Section V. The mass spectra are characteristic of aromatic compounds: large molecular ion peaks and an abundance of doubly charged ions. Electrophilic substitution is predicted and found to occur in position 5 (**49**) and 6 (**50a**, **50b**), respectively.

V. Cycl[3,3,3]azines

Despite considerable effort,⁶⁶⁻⁷⁰ cycl[3,3,3]azine (**2**) could not be synthesized for more than a decade. The difficulties arose from the unexpected¹⁻³ instability of the parent compound. The successful synthesis took advantage of incorporating stabilizing substituents in active positions, which were removed in the final step.

A. SYNTHESIS

The parent cyclazine **2a** was obtained from 4-chloroquinolizinium perchlorate by the route outlined in Scheme 3. Under nitrogen it is stable as a brown crystalline solid, but it decomposes within minutes when exposed to air or when dissolved in CHCl₃, CCl₄, or hydroxylic solvents.⁴

⁶⁴ O. Ceder and B. Beijer, *Tetrahedron* **30**, 3657 (1974).

⁶⁵ O. Ceder and B. Beijer, *Tetrahedron* **32**, 173 (1976).

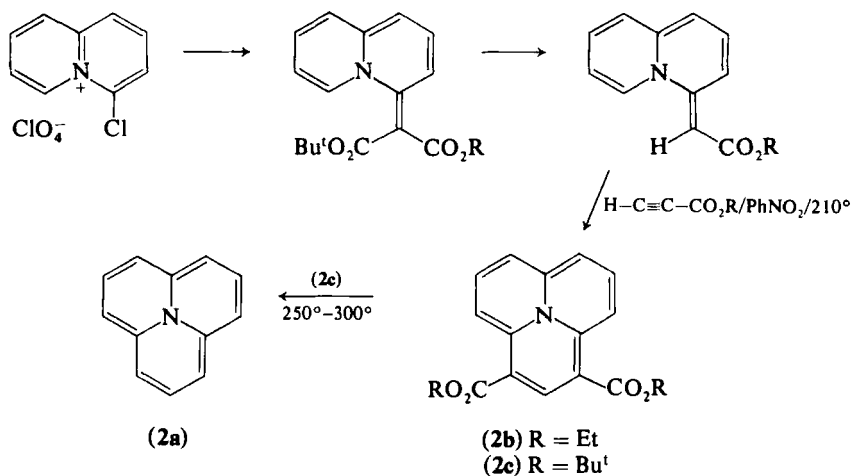
⁶⁶ V. Boekelheide and W. G. Gall, *J. Org. Chem.* **19**, 499 (1954).

⁶⁷ H. V. Hansen and E. D. Amstutz, *J. Org. Chem.* **28**, 393 (1963).

⁶⁸ V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron* **20**, 33 (1964).

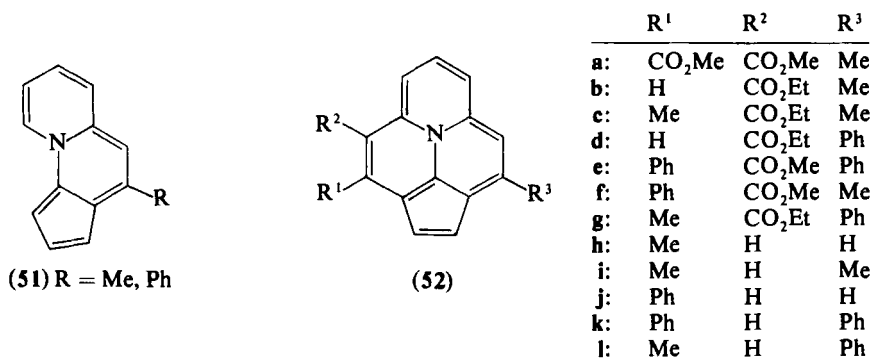
⁶⁹ D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1629 (1965).

⁷⁰ G. R. Underwood, *J. Org. Chem.* **33**, 1313 (1968).



SCHEME 3

Cyclopenta[*c*]quinolizines (**51**) reacted with acetylenic esters in boiling nitrobenzene to give cyclopenta[*cd*]cycl[3,3,3]azines (**52**). Other media were found to be ineffective, even in the presence of palladium-charcoal. The alkoxycarbonyl groups of the esters were readily removed by alkaline hydrolysis followed by vacuum pyrolysis of the resulting acids.^{71,72}



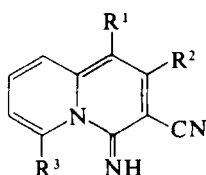
Numerous azacycl[3,3,3]azines have been prepared containing nitrogen atoms in the stabilizing 1(3)-positions of the periphery.

The 1-azacycl[3,3,3]azines (**54a, b**) were obtained from the reaction of dialkyl acetylenedicarboxylates and the quinolizine derivatives (**53a, b**) which resulted from reaction of 2-pyridinoacetonitrile with 2-

⁷¹ W. K. Gibson and D. Leaver, *J. Chem. Soc., Chem. Commun.*, 11 (1965).

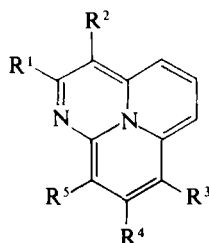
⁷² R. P. Cunningham, D. Farquhar, W. K. Gibson, and D. Leaver, *J. Chem. Soc. C*, 239 (1969).

cyano-3-ethoxyacrylonitrile and 2-cyano-3,3-bis(methylthio)acrylonitrile, respectively.⁷³ The reaction of 4-imino-4*H*-quinolizine derivatives (**53c,d**) with acetic anhydride gave the 2-methyl-1-aza derivatives (**54c,d**). Compound **54e** was transformed into the hydrobromide of 2-methyl-1-azacycl[3,3,3]azine (**54f**) by heating with polyphosphoric acid followed by refluxing in 48% hydrobromic acid. The free base (**54f**) was obtained in crude form with potassium carbonate. Purification proved to be difficult, since **54f** is very unstable.⁷⁴⁻⁷⁶



(53)

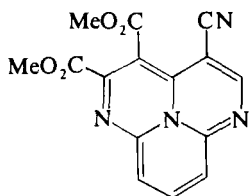
- a: $R^1 = \text{CN}; R^2 = R^3 = \text{H}$
 b: $R^1 = \text{CN}; R^2 = \text{SMe}; R^3 = \text{H}$
 c: $R^1 = \text{CN}; R^2 = \text{H}; R^3 = \text{Me}$
 d: $R^1 = \text{CO}_2\text{Et}; R^2 = \text{H}; R^3 = \text{Me}$



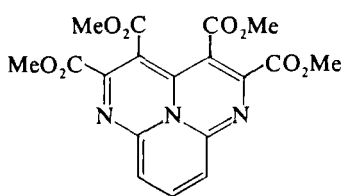
(54)

- a: $R^1 = R^2 = \text{CO}_2\text{Me}; R^3 = R^5 = \text{CN}; R^4 = \text{H}$
 b: $R^1 = R^2 = \text{CO}_2\text{Me}; R^3 = R^5 = \text{CN}; R^4 = \text{SMe}$
 c: $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = R^5 = \text{CN}$
 d: $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = \text{CO}_2\text{Et}; R^5 = \text{CN}$
 e: $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = \text{CO}_2\text{Me}; R^5 = \text{CN}$
 f: $R^1 = \text{Me}; R^2 = R^3 = R^4 = R^5 = \text{H}$

The reaction of 4-cyano-1,3,6-triazacycl[3,3,3]azine (**58d**) with dimethyl acetylenedicarboxylate yielded the 1,6-diazacycl[3,3,3]azines **55a** (solvent DMF) and **55b** (solvent acetonitrile).⁷⁷



(55a)



(55b)

⁷³ G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, C. Maseda, and H. Awaya, *Yakugaku Zasshi* **94**, 50 (1974).

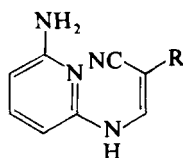
⁷⁴ H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **22**, 1424 (1974).

⁷⁵ H. Awaya, C. Maseda, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **22**, 1939 (1974).

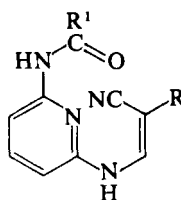
⁷⁶ G. Kobayashi, Y. Matsuda, Y. Tominaga, C. Maseda, H. Awaya, and K. Kurata, *Chem. Pharm. Bull.* **23**, 2759 (1975).

⁷⁷ K. Kurata, M. Matsuo, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **23**, 1629 (1975).

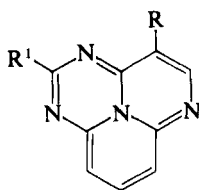
The sequence for the synthesis of 1,3,6-triazacycl[3,3,3]azines (**58**) is based on the reaction of 2,6-diaminopyridine with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate, leading to compounds **56**. These on acylation gave **57**, which after cyclodehydration yielded the desired cyclazines (**58**). Small amounts of the unsubstituted parent triazacyclazine (**58a**) were observed when the cyclization of **57** was carried out in a refluxing mixture of biphenyl and diphenyl ether. Decyanation of 4-cyano-2-methyl-1,3,6-triazacycl[3,3,3]azine (**58f**) with polyphosphoric acid at 200° yields 2-methyl-1,3,6-triazacycl[3,3,3]azine (**58b**).⁷⁸⁻⁸⁰ The synthesis of **58d** was carried out by a closely related route.⁷⁴



(56)

R = CN, CO₂Et

(57)

R = CN; CO₂Et
R¹ = H, Me

(58)

a: R = R¹ = H
b: R = H; R¹ = Me
c: R = CO₂Et; R¹ = H
d: R = CN; R¹ = H
e: R = CO₂Et; R¹ = Me
f: R = CN; R¹ = Me

Tribenzo-1,4,7-triazacycl[3,3,3]azine ("tricycloquinazoline") (**59**) has been shown to be carcinogenic for mouse skin.⁸¹ It was synthesized in a number of ways starting with anthranilic acid derivatives^{82,83} or with anthranil.⁸⁴ Hydroxy derivatives and [¹⁴C]tricycloquinazoline were

⁷⁸ O. Ceder and J. E. Andersson, *Acta Chem. Scand.* **26**, 596 (1972).

⁷⁹ O. Ceder, J. E. Andersson, and L.-E. Johansson, *Acta Chem. Scand.* **26**, 624 (1972).

⁸⁰ O. Ceder and K. Vernmark, *Acta Chem. Scand.* **27**, 3259 (1973).

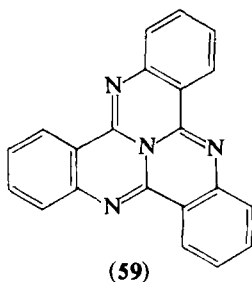
⁸¹ R. W. Baldwin, C. J. Cunningham, and M. W. Partridge, *Brit. J. Cancer* **13**, 94 (1959).

⁸² M. W. Partridge, H. J. Vipond, and J. A. Waite, *J. Chem. Soc.*, 2549 (1962).

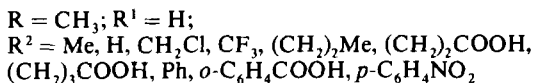
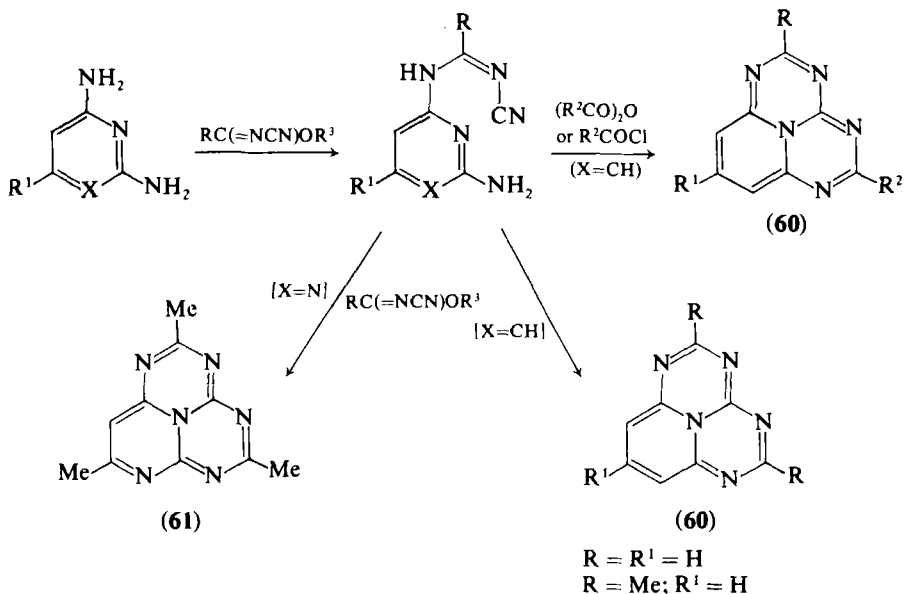
⁸³ S. C. Pakrashi, *J. Org. Chem.* **36**, 642 (1971).

⁸⁴ F. Yoneda and K. Mera, *Chem. Pharm. Bull.* **21**, 1610 (1973).

prepared for studies of the metabolism and mechanism of its carcinogenic action.⁸⁵



1,3,4,6-Tetraazacycl[3,3,3]azines (**60**) and 2,5,8-trimethyl-1,3,4,6,7-pentaazacycl[3,3,3]azine (**61**) have been prepared according to Scheme 4.^{86,87}



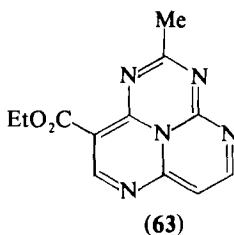
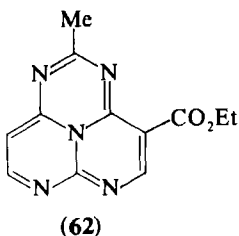
SCHEME 4

⁸⁵ H. G. Dean, R. J. Grout, M. W. Partridge, and H. J. Vipond, *J. Chem. Soc. C*, 142 (1968).

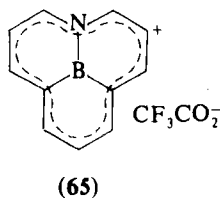
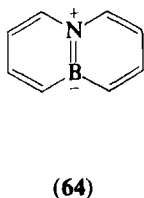
⁸⁶ J. T. Shaw, W. M. Westler, and B. D. Stefanko, *J. Chem. Soc., Chem. Commun.*, 1070 (1972).

⁸⁷ J. T. Shaw, M. E. O'Connor, R. C. Allen, W. M. Westler, and B. D. Stefanko, *J. Heterocycl. Chem.* **11**, 627 (1974).

The 1,3,6,7-tetraazacycl[3,3,3]azine (**62**)⁸⁸ and its isomer (**63**)⁸⁹ have been obtained by procedures similar to those for the preparation of triazacycl[3,3,3]azines (**58**).



The reaction of 9,10-borazonaphthalene (**64**) with malondialdehyde bisdiethylacetal in trifluoroacetic acid yields a violet product. Its spectroscopic properties are in agreement with structure **65**, which is closely related to that of the cycl[3,3,3]azines, but attempts to isolate a solid salt were unsuccessful.⁹⁰



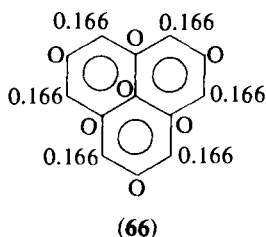
B. PHYSICOCHEMICAL PROPERTIES

Cycl[3,3,3]azine (**2**), although isoelectronic with the stable phenalene anion (**66**),^{2,3} is apparently not aromatic. Calculations using a semi-empirical self-consistent field (SCF) MO method indicate that it should be antiaromatic with alternating bond lengths. This can be understood in terms of PMO theory: the distribution of the negative charge in the phenalene anion (**66**) corresponds to that of the nonbonding molecular orbital. Cyclazine (**2**) is derived from **66** by replacing the central carbon atom by the isoelectronic N⁺. This situation is obviously unsatisfactory energetically, since the resulting structure is zwitterionic. As a consequence, the π -electrons must polarize to compensate the nitrogen atom positive charge, thus destroying the delocalization responsible for aromaticity. Cycl[3,3,3]azine (**2**) is therefore more closely related to [12]annulene than to the phenalene anion (**66**).⁶

⁸⁸ O. Ceder and J. F. Witte, *Acta Chem. Scand.* **26**, 635 (1972).

⁸⁹ O. Ceder and K. Rosén, *Acta Chem. Scand.* **27**, 2421 (1973).

⁹⁰ M. J. S. Dewar and R. Jones, *Tetrahedron Lett.*, 2707 (1968).



HMO charge densities of phenalene

According to PMO theory, the destabilizing influence of the central nitrogen atom in **2** may be compensated by an enhancement of the electronegativity at the positions of highest electron density. One would expect an increasing resemblance to the delocalized phenalene anion (**66**) in going from the parent cyclazine (**2**) to azacycl[3,3,3]azines as well as to ester derivatives of **2** that cause perturbations in positions 1,3 ... etc. This is demonstrated in Table III, using the REPE values of Hess and Schaad.^{5,91}

The chemical shifts of the ring protons of cycl[3,3,3]azine (**2a**) are among the highest reported for protons joined to trigonal carbon atoms. The signals are 2.2 and 2.8 ppm upfield of their counterparts in the spectrum of 1-phenyl-1,2-dihydropyridine.⁴ This high degree of shielding

TABLE III
RESONANCE ENERGY PER ELECTRON (REPE VALUES⁵) OF CYCL[3,3,3]AZINES^a

Cycl[3,3,3]azine	$E_{\pi}(\beta)$	$E_{\text{add}}(\beta)$	REPE(β)
Unsubstituted	16.424	16.197	0.0162
1-Aza- ^b	15.872	15.519	0.0252
		15.546	0.0232
1,3-Diaza-	15.259	14.828	0.0279
1,3,6-Triaza- ^b	14.629	14.180	0.0314
		14.217	0.0295
1,3,4,6-Tetraaza	13.960	13.446	0.0368
1,3,4,7-Tetraaza ^b	13.969	13.512	0.0326
		13.566	0.0288
1,3,6,7-Tetraaza	13.972	13.539	0.0309
1,3,4,6,7-Pentaaza	13.290	12.861	0.031
		12.888	0.029
2-Aza-	15.640	15.491	0.0107
2,5-Diaza-	14.856	14.785	0.005

^a $h_N = 0.38 \beta$; $k_{C=N} = 0.70 \beta$; $h_N = 1.5 \beta$; $k_{C=N} = 0.9 \beta$.

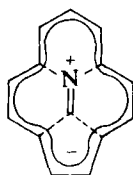
^b Two localized structures with different E_{add} values may be drawn.

⁹¹ W. Flitsch, E. R. Gesing, and J. Koszinowski, unpublished results. Recalculating, we find for **2** REPE = 0.0162 β instead of 0.001 β given in the literature.⁵

is evidence of a paramagnetic ring-current in the 12- π periphery which is in agreement with the MO treatment mentioned earlier. MO calculations also account well for the chemical shifts (δ 1H = 2.07, δ 2H = 3.65), which imply that the π -electron density differs significantly between these positions.⁶

Ester groups and/or nitrogen atoms in the positions 1,3 ... etc. of the periphery cause the expected deshielding effect. While the degree of deshielding is not regarded as evidence of aromatic properties in compound **54**,⁷⁵ **58b**, and **62** are definitely diatropic.^{78,88} A comparison of the PMR spectra of **58b** in CDCl₃ and trifluoroacetic acid shows the influence of N-protonation to be comparable to a perturbation caused by both a nitrogen atom and an ester group.

The PMR spectra indicate strong differences between the paratropic cycl[3,3,3]azines (**2**) and the cyclopentacyclazines (**52**), which are unequivocally diatropic compounds (Table IV). The five-membered ring double bonds have been shown to be delocalized by the vicinal coupling constants of the corresponding protons.^{71,72} These observations suggest that cyclopentacycl[3,3,3]azines (**52**) are best considered as [13]annulene anions weakly coupled to a strong localized central azomethinium cross-link represented as in **67**. A study of some acephenalene derivatives isoelectronic with **67** has led to similar conclusions.^{92,93}



(67)

The mutual interaction between the two closed-shell systems is small since the bonding MO's of the peripheral [13]annulene can interact only with the antibonding MO of the azomethine (ethylene) group by reason of symmetry.⁹¹

A simple model which correlates the HOMO and LUMO of cycl[3,3,3]azine with the degenerate nonbonding orbitals of [12]annulene accounts for the ESR spectra of the radical cations and anions of **2a** and some derivatives. This model also predicts the almost identical π -spin population observed for the **2a**-cation and the isoelectronic phenalenyl

⁹² I. Murata, K. Yamamoto, T. Hirotsu, and M. Morioka, *Tetrahedron Lett.*, 331 (1972).

⁹³ I. Murata, K. Imamoto, M. Morioka, M. Tamura, and T. Hirotsu, *Tetrahedron Lett.*, 2287 (1975).

TABLE IV
PROTON MAGNETIC RESONANCE SPECTRA OF CYCL[3,3,3]AZINES (δ -VALUES, TMS STANDARD)

No.		1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	J (Hz)	Solvent	References
2a	—	2.07	3.65	2.07	2.07	3.65	2.07	2.07	3.65	2.07	$J_{12} = 8$	Bis(trimethylsilyl)ether	4
2b	1,3-Di-CO ₂ Et	—	7.16 (7.09)	—	6.77 (6.68)	6.14 (6.08)	5.23 (5.21)	5.23 (5.21)	6.14 (6.08)	6.77 (6.68)	$J_{45} = J_{36} = 8$ $J_{46} = 1.7$	Not given CDCl ₃	4 4
54f	2-Me-1-Aza-	—	(1.02)	3.71	Not correlated: 5-, 7-H: 5.40, 5.64, 4-, 6-, 8-, 9-H: 3.84, 4.24, 4.28, 4.54						All $J = 8$	CDCl ₃	75
58b	2-Me-1,3,6-triaza	—	(1.67) (2.27)	—	4.97 6.28	7.07 8.15	—	5.81 7.23	6.77 7.97	5.35 6.81	No J given No J given	CDCl ₃ CF ₃ COOH	80
62	2-Me-4-CO ₂ Et 1,3,6,7-tetraaza	—	(2.1)	—	—	8.22	—	—	7.75	5.76	$J_{89} = 5$	CDCl ₃	88
Cyclopenta[cd]cycl[3,3,3]azines (52)													
52h	3-Me	6.96	6.96	(2.38)	6.27	—	—	—	6.41	7.51	$J_{89} = 8$	CS ₂	71, 72
52i	3,9-Di-Me	6.96	6.96	(2.39)	6.29	6.66	6.95	6.66	6.29	(2.39)	$J_{34} = (0.7)$; $J_{56} = J_{67} = 8.0$; $J_{89} = (0.7)$	CS ₂	71, 72

radical. In contrast to the neutral cyclazine (**2a**), the corresponding cation and anion are not considered to exhibit bond alternation.⁹⁴ According to MINDO/3 calculations, addition or removal of an electron should lead to little structural change in the phenalenyl radical.⁹⁵

The mass spectra of 1,3,6-triazacycl[3,3,3]azines (**58**) have been studied in detail.⁹⁶

C. CHEMICAL PROPERTIES

Catalytic hydrogenation of **2b** yielded the tetrahydro derivative **68**. One *t*-butoxycarbonyl group was removed selectively from the diesters (**2c**, **2d**, and **2e**) above 220°. Dimethyl acetylenedicarboxylate in boiling benzene converted **2b** into the red Diels–Alder adduct **69a**. This readily formed a dihydro derivative (**69b**), which lost ethylene above 220° to give **2f**.

Electrophilic substitution of the cyclazine diester **2b** gave 4- and/or 6-substituted derivatives: typical examples are the two aldehydes (**2h** and **2i**) obtained by Vilsmeier formylation and the 4- and 6-nitro derivatives (**2j** and **2k**) resulting from a brief treatment of **2b** with copper(II) nitrate in acetic anhydride.

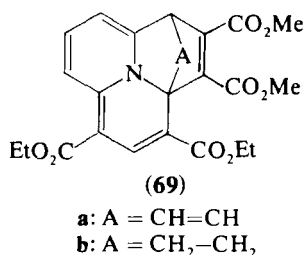
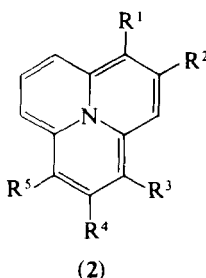
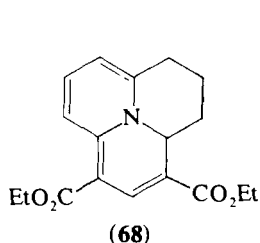
The cyclazine monoester **2g** is much more reactive than the diester and electrophilic substitution is accompanied by extensive tar formation. The Vilsmeier reaction afforded two chromatographically mobile products, which gave similar mass spectra showing parent ions corresponding to monoformyl derivatives. The major product was identified as the 3-formyl derivative (**2h**). Attempts were made to nitrate **2l** and to formylate and acetylate the parent cyclazine (**2a**), but decomposition was extensive and no product could be isolated.⁴ Treatment of a solution of **2a** in benzene with bromine vapor gave the stable blue cyclazine cation bromide, which was converted on further treatment with bromine into the greenish brown dication dibromide. Blue solids presumed to be radical cation salts of **2b** were less stable and were transformed into diazoniadibenzo[*cd,lm*]perylene (**70**) on heating in benzene–ethanol.⁴

Protonation and proton–deuteron exchange was shown to occur in position 1 of the cyclopentacyclazine (**52i**). Benzoylation could be achieved at the same position by heating with benzoyl chloride in the presence of solid sodium carbonate.^{71,72} Electrophilic bromination of

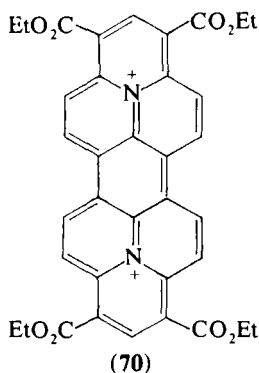
⁹⁴ F. Gerson, J. Jachimowicz, and D. Leaver, *J. Am. Chem. Soc.* **95**, 6702 (1973).

⁹⁵ R. C. Haddon, *Aust. J. Chem.* **28**, 2343 (1975).

⁹⁶ O. Ceder and J. E. Andersson, *Acta Chem. Scand.* **26**, 611 (1972).



- a: R¹ = R² = R³ = R⁴ = R⁵ = H
b: R¹ = R² = CO₂Et; R³ = R⁴ = R⁵ = H
c: R¹ = R² = CO₂Bu^t; R³ = R⁴ = R⁵ = H
d: R¹ = CO₂Me; R² = CO₂Bu^t; R³ = R⁴ = R⁵ = H
e: R¹ = CO₂Et; R² = CO₂Bu^t; R³ = R⁴ = R⁵ = H
f: R¹ = R² = CO₂Et; R³ = R⁴ = CO₂Me; R⁵ = H
g: R¹ = CO₂Et; R² = R³ = R⁴ = R⁵ = H
h: R¹ = R² = CO₂Et; R³ = CHO; R⁴ = R⁵ = H
i: R¹ = R² = CO₂Et; R³ = R⁴ = H; R⁵ = CHO
j: R¹ = R² = CO₂Et; R³ = NO₂; R⁴ = R⁵ = H
k: R¹ = R² = CO₂Et; R³ = R⁴ = H; R⁵ = NO₂
l: R¹ = CO₂Et; R² = CHO; R³ = R⁴ = R⁵ = H



1,3,6-triazacycl[3,3,3]azine (**58a**) takes place preferentially in position 4. On further bromination and in case of substitution, 4-cyano-2-methyl-1,3,6-triazacycl[3,3,3]azine (**58f**), positions 7 and 9 are attacked.^{79,97} Reaction of **58f** with free bromine, and with thiocyanogen in the presence of light, results in ring as well as side-chain substitution.⁹⁸ Reactions of substituted tetraazacycl[3,3,3]azines **62** and **63** with *N*-bromosuccinimide result in electrophilic attack at positions that have been predicted from arguments using resonance structures and HMO calculations.^{89,99} Brominated 4-cyano-2-methyl-1,3,6-triazacycl[3,3,3]-azines could be decyanated by treatment with polyphosphoric acid. The

⁹⁷ O. Ceder and M. L. Samuelsson, *Acta Chem. Scand.* **27**, 3264 (1973).

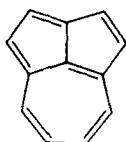
⁹⁸ O. Ceder and M. L. Samuelsson, *Acta Chem. Scand.* **27**, 2095 (1973).

⁹⁹ O. Ceder and K. Rosén, *Acta Chem. Scand.* **27**, 359 (1973).

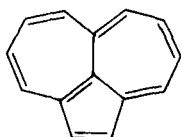
reaction has been used to establish the structure of dibromo-1,3,6-triazacycl[3,3,3]azines.¹⁰⁰

VI. Cycl[4,2,2]azines

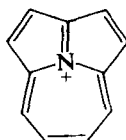
An increase in electronegativity of the central atom of cyclopent[*cd*]-azulene (71) will bring about a decrease in energy of the HOMO, leaving the LUMO unaffected. A similar perturbation at the central atom of aceheptylene (72), on the other hand, should not alter the energy of the HOMO, but lower that of the LUMO.



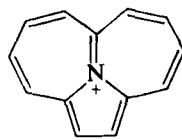
(71)



(72)



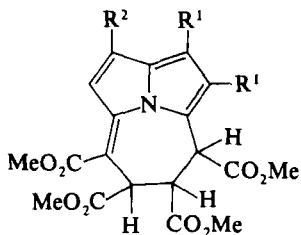
(73)



(74)

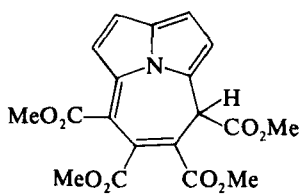
As a consequence, the properties of the ions 73 and 74 should differ much more than those of the known isoconjugates 71¹⁰¹ and 72.¹⁰² The cycl[4,2,2]azinium salts (73) presumably will be diatropic stable compounds.

Salts of the type 73 and 74 are as yet unknown. Tetramethyl 5,6-dihydro-7*H*-cycl[4,2,2]azinetetracarboxylates (75) have been obtained by reaction of 3*H*-pyrrolizines (25) with excess of dimethyl acetylenedicarboxylate.



(75)

- a: $R^1 = R^2 = H$
 b: $R^1 = Me; R^2 = H$
 c: $R^1 = H; R^2 = Me$

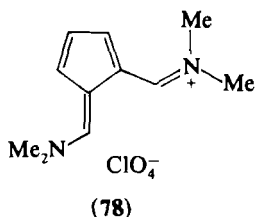
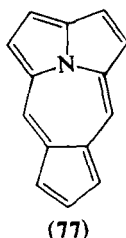


(76)

¹⁰⁰ O. Ceder and M. L. Samuelsson, *Acta Chem. Scand, Ser. B* **29**, 867 (1975).

¹⁰¹ K. Hafner, K.-P. Meinhardt, and W. Richarz, *Angew. Chem.* **86**, 235 (1974); *Angew. Chem., Int. Ed. Engl.* **13**, 204 (1974).

¹⁰² K. Hafner, *Pure Appl. Chem.* **28**, 163 (1971).



Compound **75a** was readily dehydrogenated to give the *5H*-cyclo[4,2,2]azine derivative **76**, but attempts to oxidize **76** were unsuccessful.¹⁰³

Treatment of bis(dimethylaminomethylene)pyrrolizinium perchlorate (**29**) with cyclopentadiene-NaH in DMF gave the diatropic cyclopenta-*[h]*cyclo[4,2,2]azine (**77**), which was also obtained from the fulvene derivative (**78**) and 3*H*-pyrrolizine (**25**). Electrophilic substitutions (deuteration, nitration, nitrosation, acylation, bromination, Mannich reaction) occur in the 6- and 8-positions.³²

The electronic absorption spectrum of **77** is similar to that of azulene.³² This similarity also holds for the ESR spectra of the corresponding anions.⁵⁴

VII. Cycl[4,3,2]azines

Cycl[4,3,2]azines and cycl[3,3,3]azines are N-bridged [12]annulenes having different points of attachment to the central nitrogen atom. A study of topological influences in these π -systems seems feasible by a comparison of the properties of related derivatives.

A. SYNTHESIS

Wittig reactions with pyrrole-2-aldehyde led to the esters (**79**) which were cyclized to 3a-azaazulen-4-ones (**80**).^{104, 105} 4-Methylene-3a-azaazulenes (**81**) have been obtained from **80** with stabilized phosphoranes.³⁶ Reaction of dimethyl acetylenedicarboxylate with **81** could not be achieved. A similar cycloaddition was successful in the synthesis of cycl[3,3,3]azines (**2**) (Section V).

The azaazulene **81a** reacted with oxalyl chloride in benzene to give **82**, which is insoluble in all conventional solvents.¹⁰⁶

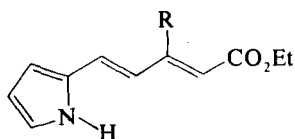
¹⁰³ D. Johnson and G. Jones, *J. Chem. Soc., Perkin Trans. 1*, 844 (1972).

¹⁰⁴ W. Flitsch, B. Mütter, and U. Wolf, *Chem. Ber.* **106**, 1993 (1973).

¹⁰⁵ E. Mukidjam, Diplomarbeit, Münster 1975.

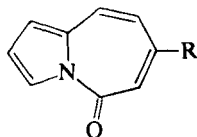
¹⁰⁶ W. Flitsch and B. Mütter, *Angew. Chem.* **85**, 543 (1973); *Angew. Chem., Int. Ed. Engl.* **12**, 501 (1973). W. Flitsch, A. Gurke, and B. Mütter, *Chem. Ber.* **108**, 2969 (1975).

Vilsmeier reaction of the 3a-azaazulenones (**80**) yielded the aldehydes (**83**). Wittig reaction converted **83** into the esters (**84**), which could be cyclized to cycl[4,3,2]azines (**85**) by a pyridine-piperidine mixture.¹⁰⁵⁻¹⁰⁷



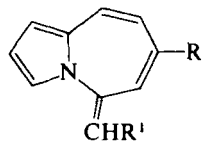
(79)

a: R = H
b: R = Me
c: R = Bu^t



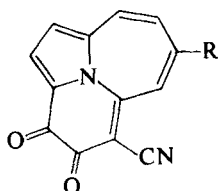
(80)

a: R = H
b: R = Me
c: R = Bu^t



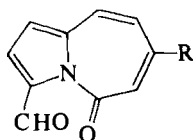
(81)

a: R = H; R¹ = CN
b: R = H; R¹ = CO₂Et
c: R = Me; R¹ = CN



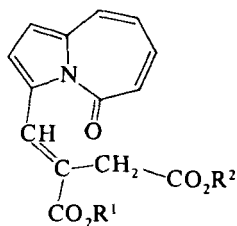
(82)

a: R = H
b: R = Me

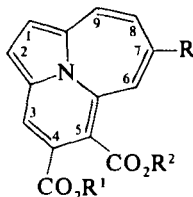


(83)

a: R = H
b: R = Me



(84)



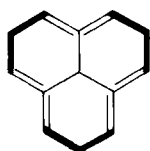
(85)

a: R = H; R¹ = R² = Et
b: R = H; R¹ = Me; R² = Et
c: R = H; R¹ = R² = Bu^t
d: R = Me; R¹ = R² = Et
e: R = Me; R¹ = R² = Bu^t
f: R = R¹ = H; R² = Et

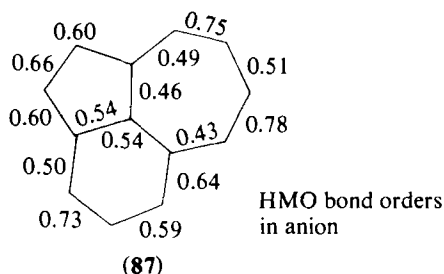
¹⁰⁷ B. Müter, Dissertation, Münster, 1974.

B. PHYSICOCHEMICAL PROPERTIES

The topological difference between cycl[3,3,3]azine (**2**) and cycl[4,3,2]azine (**85**) follows from a comparison of the isoelectronic anions (**86**) and (**87**) using HMO calculations.¹⁰⁸ Since the HOMO's of **86** and **87** are nonbonding, anions, cations, and radicals are of comparable stability. Charge density and bond orders of the cation and anion of **86** depend on the symmetry of the molecule: the (positive or negative) charges are located in the "starred" positions (1,3 ...). There are three different bond orders, as shown in formula **86**.



(86)



(87)

Charge distributions and bond orders of the cation and anion of 2*H*-benz[*cd*]azulene, on the other hand, are dissimilar. The seven-membered ring of the cation is delocalized, containing most of the positive charge, while that of the anion **87** is localized and the negative charge resides mainly in the delocalized indenyl moiety. A delocalized indolizine part with a localized butadiene bridge in the isoelectronic cycl[4,3,2]azine (**85**) would ensue from a similar topological control. This has been confirmed by SCF calculations.¹⁰⁹

The failure of resonance stabilization (REPE values for cycl[4,3,2]azine: 0.0038 β ; for **2a**: 0.0162 β) as well as the small difference in energy of HOMO and LUMO (0.29 β for cycl[4,3,2]azine; 0.55 β for **2a**) point to the instability of the parent compound,⁹¹ which has not yet been obtained.

The PMR spectrum of **85a** agrees well with theoretical considerations. It can be seen from the vicinal coupling constants that the seven-membered ring is planar, containing localized bonds. A paratropic effect of 1.7 ppm in the five- and six-membered rings and one of at least 2.7 ppm in the seven-membered ring follows from comparison with suitable reference compounds. The different paratropism can be explained by the superposition of two ring systems, a diatropic indolizine and a paratropic [12]annulene moiety.^{106,107}

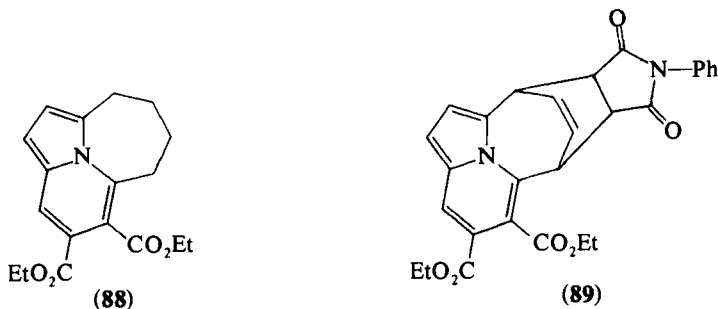
¹⁰⁸ A. Streitwieser and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations." Pergamon, New York, 1965: (a) phenalene, p. 272; (b) benz[*cd*]azulene, p. 267.

¹⁰⁹ R. Kuhrke, Staatsarbeit, Münster, 1973.

C. CHEMICAL PROPERTIES

Hydrogenation of **85a** gives the tetrahydro derivative (**88**). A cycloadduct (**89**) may be obtained with *N*-phenylmaleimide. Heating **85a** in toluene results in formation of a dimer containing two indolizine parts easily distinguished one from the other by PMR spectroscopy.

Hydrolysis and transesterification of **85a** result in the ester acid (**85f**) and the mixed ester (**85b**), respectively. The ester group in the 5-position has been shown to be severely hindered and is not coplanar with the ring system. Attempts to remove functional groups by thermolysis of **85c**, **85e**, and **85f** failed, decomposition taking place instead.^{106, 107}

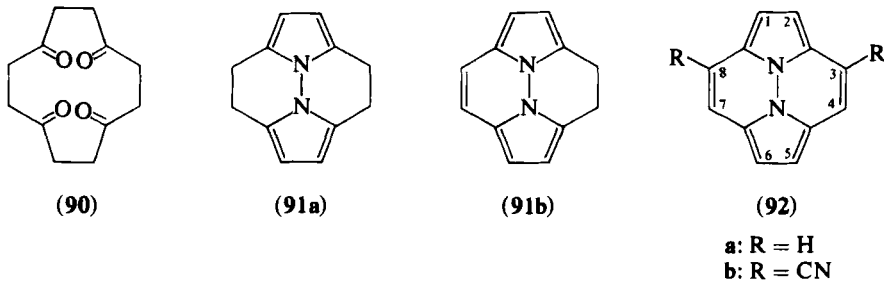


VIII. Hydrazino-Bridged Annulenes

A. 8b,8c-DIAZAPYRACYLENES

1. Synthesis

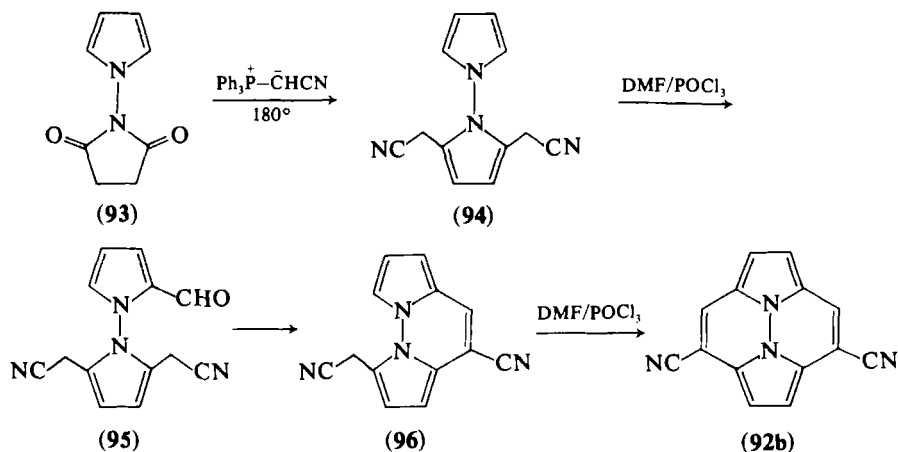
The parent compound (**92a**) has been synthesized from the tetraketone (**90**). Addition of hydrazine afforded the locked metaheterocyclophane (**91a**). Conversion of **91a** to **91b** could be accomplished by palladium-on-charcoal, further dehydrogenation to **92a** requiring palladium-on-charcoal in nitrobenzene or DDQ in toluene.^{110, 111}



¹¹⁰ W. W. Paudler and E. A. Stephan, *J. Am. Chem. Soc.* **92**, 4468 (1970).

¹¹¹ J. L. Atwood, D. E. Hrnčir, C. Wong, and W. W. Paudler, *J. Am. Chem. Soc.* **96**, 6132 (1974).

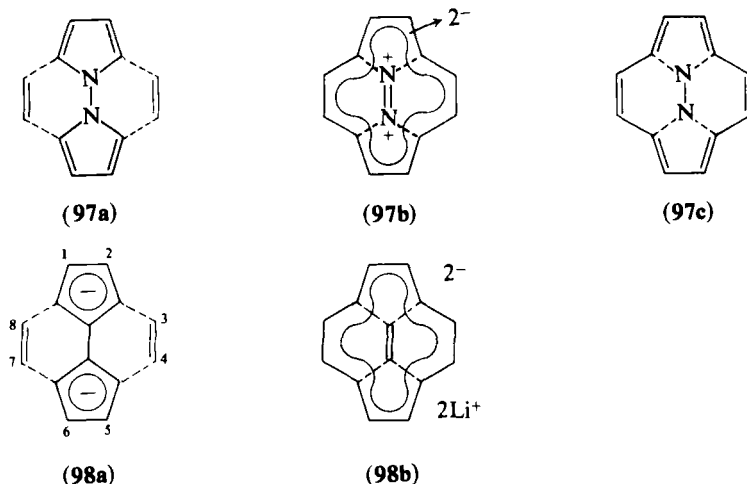
Scheme 5 shows another synthetic sequence, which has led to the formation of 3,8-dicyano-8b,8c-diazapyracylene (**92b**).¹¹²



SCHEME 5

2. Properties

Two possible structures may be proposed for 8b,8c-diazapyracylene: an *N,N*-bipyrrolyl core with two vinyl bridges (**97a**) and a cyclodecahexaene dianion with an internal cross-linked $\text{N}=\text{N}$ unit (**97b**). A third structure **97c** has been suggested,^{110,111} which does not correlate well with the isoelectronic pyracylene dianion (**98**).



¹¹² W. Flitsch and H. Lerner, *Tetrahedron Lett.*, 1677 (1974); Unpublished results.

This dianion (**98**) is diatropic. This could indicate a structure of type **98b**¹¹³; however, SCF calculations of the stabilization energy, the bond lengths, and the charge distribution are in favor of structure **98a**.¹¹⁴

The analogous structure **97a** may be the most adequate representation for 8b,8c-diazapyracylenes since the interaction energy of the 14 π -periphery could hardly be sufficient to overcome the energy required for charge separation in **97b**.¹¹² The properties of diazapyracylenes (**92**) might be affected by a remarkable strain energy which has been calculated to be 52.6 kcal mol⁻¹ for the closely related pyracylene¹¹⁵: **92a** has been shown to be planar by X-ray analysis.¹¹¹

The 12 π -electronic periphery of 8b,8c-diazapyracylenes (**92**) should give rise to a paramagnetic ring current possibly decreased by bond-length alternation.¹¹⁶ A comparison of the PMR spectra of compounds **91a**, **91b**, and **92** (Table V) suggests a paramagnetic shift of 0.63–1.19 ppm for the pyrrole protons while the protons of the vinyl bridge experience a shielding of 1.6 ppm. The shielding of the ring protons of **92a**, however, is much smaller than that of cycl[3,3,3]azines (**2**) (shielding effect: 2.2–2.5 ppm⁴; Section V) and cycl[4,3,2]azines (**85**) (shielding effect: 1.7–2.7 ppm¹¹²; Section VII).

The ring current should decrease with increasing number of trans double bonds, thus rationalizing these differences on a qualitative basis.¹¹¹

The PMR spectra of substituted derivatives, however, provide additional evidence for the structure of bridged [12]annulenes. A comparison of **92a** and **92b** reveals a normal control of the cyano group over the chemical shift of the neighboring protons ($\Delta = 1.0$ ppm), the influence on the remote pyrrolic protons being small ($\Delta = 0.11$ –0.39 ppm). Hence diazapyracylenes should be composed of loosely connected closed-shell moieties (formula **97a**) the influence of the substituents on the chemical shift being limited to the substituted part of the molecule.¹¹²

Ester groups, on the other hand, exert a strong effect on the shift of *all* protons of cycl[3,3,3]azines (**2**) ($\Delta = 2.49$ –4.70 ppm, see Table IV) thus demonstrating the greater importance of the 12 π -perimeter as outlined in Section V. The chemical properties of the 8b,8c-diazapyracylene (**92a**) are consistent with the anticipated structure. Hydrogenation takes place only in the 3,4- and 7,8-positions to give **91a** and **91b**.^{110, 111}

¹¹³ B. M. Trost, B. Buhner, and G. M. Bright, *Tetrahedron Lett.*, 2787 (1973).

¹¹⁴ D. H. Lo and M. A. Whitehead, *Chem. Commun.*, 771 (1968). Following HMO calculations, the π -electron density in position 3 of the cyclopentadiene ring is 1.003, not 1.084 as given in Trost *et al.*¹¹³

¹¹⁵ H. J. Lindner, personal communication; see also B. M. Trost, G. M. Bright, C. Frihart, and D. Britton, *J. Am. Chem. Soc.* **93**, 737 (1971).

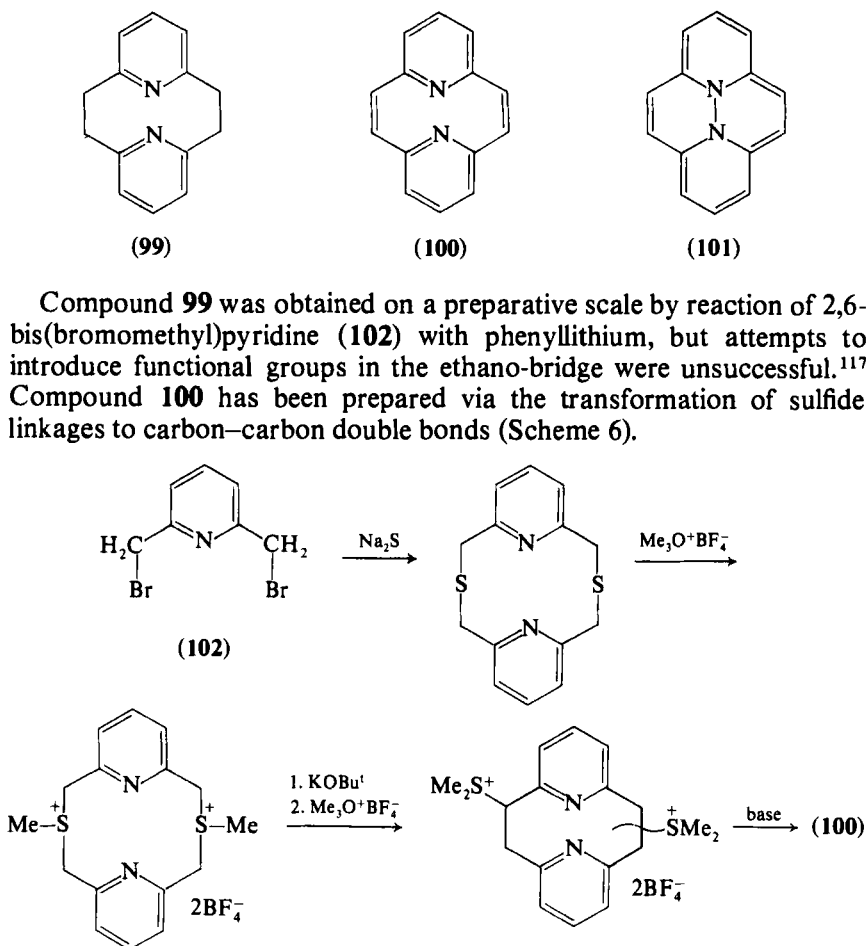
¹¹⁶ J. A. Pople and K. G. Untch, *J. Am. Chem. Soc.* **88**, 4811 (1966).

TABLE V
PROTON MAGNETIC RESONANCE SPECTRA OF 8b,8c-DIAZAPYRACYLENES

No.	Structure	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	Solvent	References
91a		5.85	5.85	2.96	2.96	5.85	5.85	2.96	2.96	CDCl ₃	111
91b		6.32	6.32	3.28	3.28	6.32	6.32	6.82	6.82	CDCl ₃	111
92a		5.13	5.13	5.22	5.22	5.13	5.13	5.22	5.22	CDCl ₃	111
92b		5.33	5.33	—	6.18	5.52	5.52	6.18	—	DMSO-d ₆	112
a: R = H b: R = CN											

B. 10b,10c-DIAZAPYRENE

The question of whether 10b,10c-diazapyrene (**101**) is capable of a finite existence has been the subject of theoretical considerations. According to HMO calculations, **100** was suggested to be the more stable valence tautomer.¹¹⁷ [2,2](2,6)Pyridinophane (**99**) was prepared in different reaction sequences by Baker *et al.* Their intention was to synthesize **100**; however, owing to lack of material, it was impossible to investigate possible routes for converting **99** into **100**.¹¹⁸



SCHEME 6

¹¹⁷ V. Boekelheide and J. A. Lawson, *J. Chem. Soc., Chem. Commun.*, 1558 (1970).

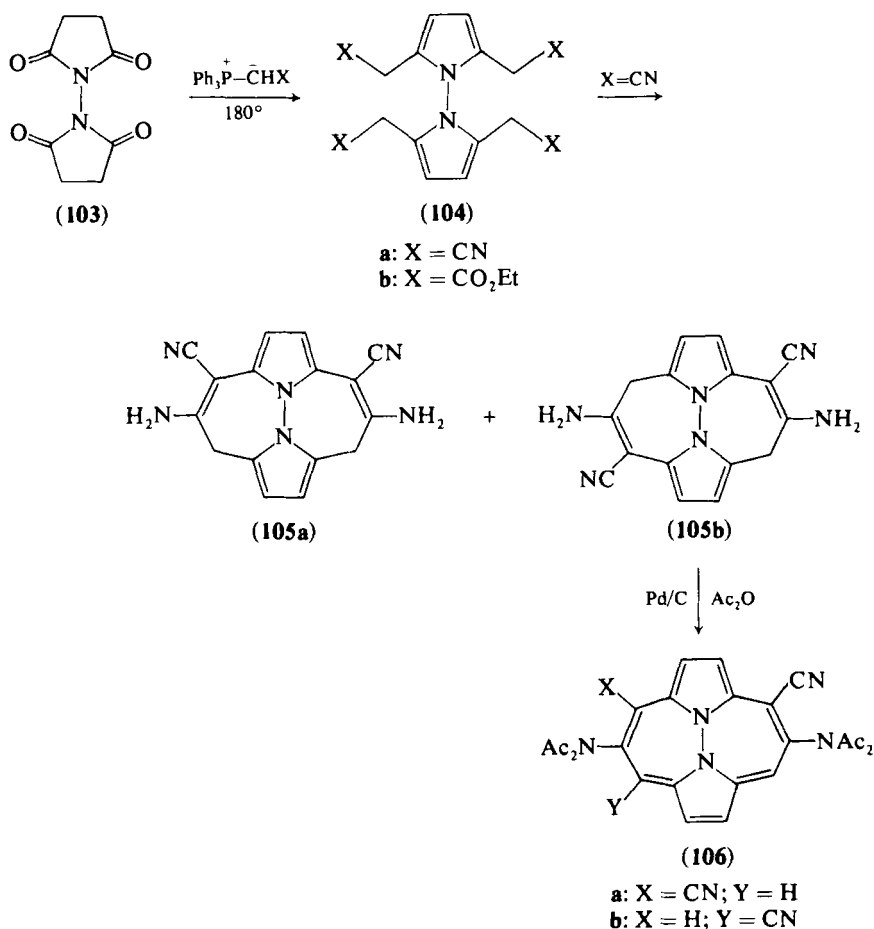
¹¹⁸ W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958).

The synthesis of **101** remains a challenge, since no indication of valence tautomerization of **100** was found.¹¹⁷

C. 10b,10c-DIAZADICYCLOPENTA(*ef,kl*)HEPTALENES
 ("DIAZAPYRACEHEPTYLENES") AND 1,4;8,11-BISIMINO[14]ANNULENES

1. *Synthesis*

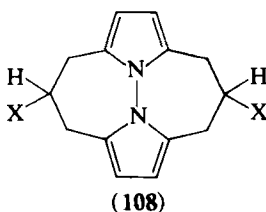
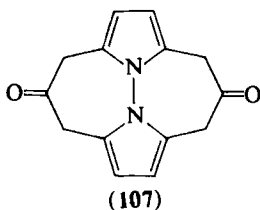
The synthesis of the diazapyraceheptylene derivatives **106a** and **106b** is depicted in Scheme 7.¹¹⁹



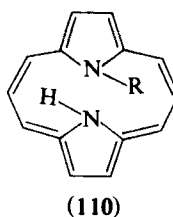
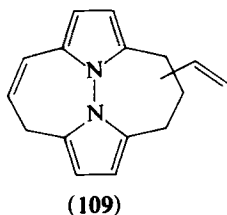
SCHEME 7

¹¹⁹ W. Flitsch and H. Peeters, *Chem. Ber.* **106**, 1731 (1973).

Dieckmann-condensation of the tetraester (**104b**) followed by hydrolytic decarboxylation yielded the diketone (**107**), which could be converted into the compounds **108**. Treatment of **108b** or **108c** with potassium *t*-butoxide in toluene gave a dihydrodiazapyraceheptylene (**109**), which rearranged on deprotonation to the unstable 1,4;8,11-bisimino[14]annulene (**110a**). N-Acetylation in acetic anhydride gave the stable acetate (**110b**). Attempts to dehydrogenate **109** to the parent diazapyraceheptylene (**106**) were unsuccessful.¹²⁰



a: X = OH
b: X = OTs
c: X = Cl



a: R = H
b: R = Ac

2. Properties

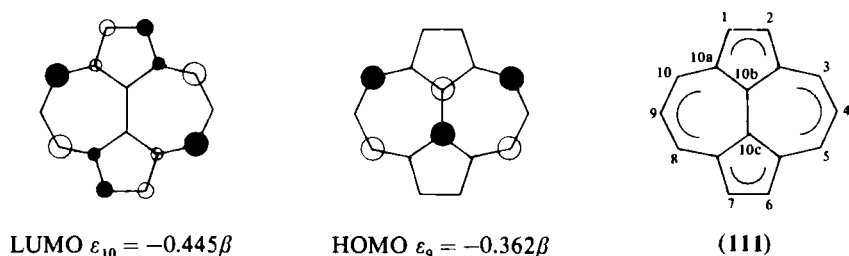
Starting with the frontier orbitals of the pyraceheptylene dianion (**111**),¹²¹ the properties of the diazapyraceheptylene (**106**) and bisimino[14]annulene (**110**) may easily be evaluated.¹²²

The HMO-calculated eigenvectors of HOMO and LUMO of **111** are shown in the formula. Perturbation of the anion by increasing electronegativity of the cross-link positions 10a and 10b, as well as opening of the cross-link itself, results in a decrease of the energy of the HOMO,

¹²⁰ W. Flitsch and H. Peeters, *Tetrahedron Lett.*, 1461 (1975).

¹²¹ Pyraceheptylene has been investigated recently: A. G. Anderson, A. A. McDonald, and A. F. Montana, *J. Am. Chem. Soc.* **90**, 2993 (1968); A. G. Anderson, G. M. Masada, and A. F. Montana, *J. Org. Chem.* **38**, 1439 (1973); A. G. Anderson, A. F. Montana, A. A. McDonald, and G. M. Masada, *ibid.* **38**, 1445 (1973); C. Jutz and E. Schweiger, *Angew. Chem.* **83**, 886 (1971); *Angew. Chem., Int. Ed. Engl.* **10**, 808 (1971); *Synthesis*, 193 (1974); see also papers by K. Hafner *et al.*, cited in these references.

¹²² W. Flitsch and H. Peeters, *Chem. Ber.* **110**, 273 (1977).



leaving the LUMO (and ψ_8) unaffected. Increasing the electronegativity in positions 3, 5, 8, and 10, on the other hand, lowers the energy of both the HOMO and the LUMO by equal amounts.

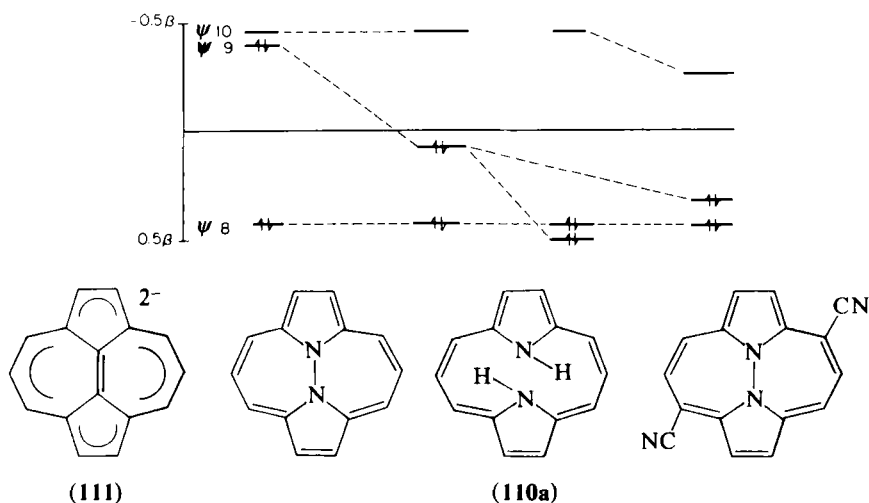
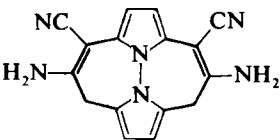
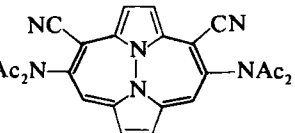
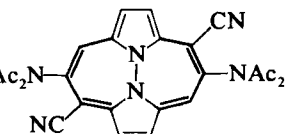
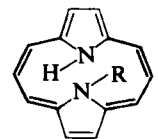


FIG. 1. π -electron energy changes of the frontier orbitals of 111^{2-} effected by N-atoms and CN-groups (HMO/PMO treatment).

The PMO treatment, a summary of which is given in Fig. 1, reflects the easy accessibility of compounds **106a**, **106b**, and **110** as well as the difficulty of dehydrogenation of **109**.

The diatropism of diazapyraceneheptylenes (**106**), which follows from a comparison of the PMR spectra with that of **105a** (Table VI), may be due to the effect of the cyano groups on the electronic configuration of the π -system. The chemical shift difference between the inside and outside protons clearly reveals the expected diamagnetic ring current in the annulene derivatives (**110**). The coupling constants of the seven-membered rings of **110** show that this part of the molecule is planar and delocalized.

TABLE VI
PROTON MAGNETIC RESONANCE (PMR) SPECTRA OF 10b,10c-DIAZAPYRACEHEPTYLENES AND BISIMINO[14]ANNULENES

No.		1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	Solvent
105a		5.98	5.98	—	—	(3.32)	5.85	5.85	(3.32)	—	—	CF ₃ COOH ^a
106a		9.41	9.41	—	—	8.83	8.80	8.80	8.83	—	—	CF ₃ COOH ^a
106b		8.82 $J_{12} = J_{67} = 5.1$ Hz	9.25	—	—	8.71	8.82	9.25	—	—	8.71	CF ₃ COOH ^a
110		a: 7.89 $\delta_{\text{NH}} = -2.1; J_{34} = J_{56} = 11.5$ Hz	7.89	8.25	7.96	8.25	7.89	7.89	8.25	7.96	8.25	CDCl ₃ /DMSO-d ₆
	a: R = H b: R = COMe	b: 7.83 $\delta_{\text{MeCO}} = -1.53; \delta_{\text{NH}}$ not observed ^b $J_{34} = J_{9,10} = 10.6$ Hz; $J_{45} = J_{89} = 11.5$ Hz	7.83	8.29	7.66	8.11	7.63/7.65	8.11	7.66	8.29	CDCl ₃ /DMSO-d ₆	

^a No substantial change to the PMR spectra in CD₃COCD₃, where the compound is very sparingly soluble

^b $\delta_{\text{NH}} = -3.1$ ppm in CDCl₃.

IX. Conclusion

Most of the compounds described here are nonalternant *and* heterocyclic. A rigorous theoretical treatment of such compounds is extremely difficult and, even for the related isoconjugate hydrocarbons, far from conclusive.¹²³ From the chemistry of cyclazines, however, it emerges that many questions in which experimentalists are interested can be answered in a satisfactory way by a PMO treatment based on simple HMO calculations.

It appears possible to deduce the properties of heterobridged annulenes from the peripheral π -system even when the heteroatoms are coplanar with the atoms in the perimeter. While this hypothesis may work in special cases, it is an oversimplification. This is outlined, e.g., in Section V, by showing that the interaction between the central nitrogen atom and the perimeter of cycl[3,3,3]azines depends on the substitution pattern. According to PMO considerations, moreover, cycl[4,4,3]azine (**4**) should be nonaromatic in spite of its 14 π -electron perimeter. The synthesis of this compound, which was suggested in the first full paper on cyclazines,¹ still remains a challenge.

ACKNOWLEDGMENT

We are grateful to Prof. Dr. Rainer Sustmann for critical comments and help in preparing the English manuscript.

¹²³ For example, the question of a paramagnetic "ring current" in pyracylene [C. A. Coulson and R. B. Mallion, *J. Am. Chem. Soc.* **98**, 592 (1976)], which is closely related to hydrazino-bridged [12]annulenes, treated in Section VIII,A.

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Quinoxaline Chemistry: Developments 1963–1975

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I. Introduction

The aim of the present review is to survey developments in the field of quinoxaline chemistry since the appearance of the previous review in this Series in 1963.¹ Interest in the chemistry of quinoxalines in the period 1963–1975 has resulted in the appearance of a large number of publications both in the journal and patent literature, and it is important to point out that the present review is intended to be selective rather than comprehensive in its coverage.

Quinoxalines are, in general, comparatively easy to prepare, and numerous derivatives have been prepared in work designed to produce biologically active materials. Quinoxaline *N*-oxides continue to be a focal point of study. Their reactions, as well as their pharmacological actions, continue to stimulate many investigations. Thus 2-methylquinoxaline *N,N'*-dioxides substituted in the 3-position (e.g., with amide,² amidino,³ hydrazinocarbonyl,⁴ and ester⁵ groups) are potent bacteriocides.

Antibiotics of the triostin and quinomycin series, isolated from

¹ G. W. H. Cheeseman, *Adv. Heterocycl. Chem.* **2**, 203 (1963).

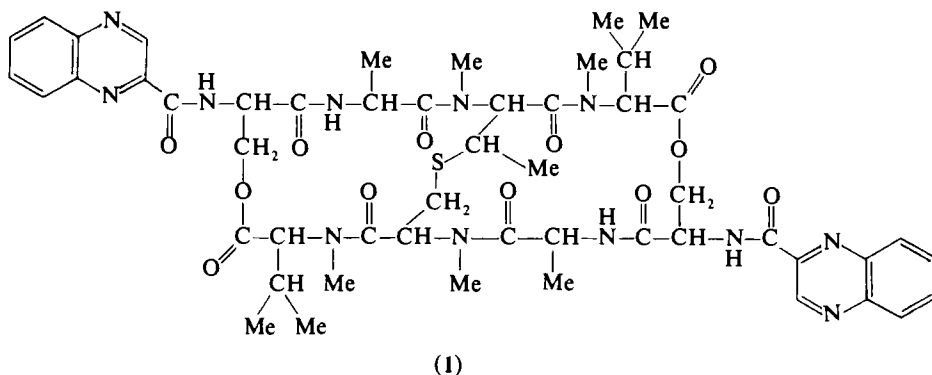
² (a) K. Ley, U. Eholzer, R. Nast, K. G. Metzger, and D. Fritsche, S. African Patent 68 06,099 [CA 71, 91528 (1969)]; (b) R. Nast, K. Ley, U. Eholzer, K. G. Metzger, and D. Fritsche, S. African Patent 69 05,597 [CA 73, 120671 (1970)].

³ K. Ley, U. Eholzer, K. G. Metzger, and D. Fritsche, S. African Patent 68 06,094 [CA 72, 3508 (1970)].

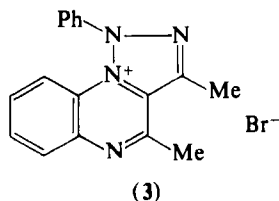
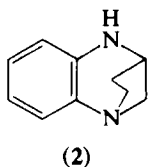
⁴ (a) W. Duerckheimer and E. Schrinner, S. African Patent 69 04,857 [CA 73, 35402 (1970)]; (b) W. Duerckheimer, H. Hartung, and E. Schrinner, Ger. Offen, 2,002,712 (1971) [CA 75, 98595 (1971)].

⁵ R. V. Kasubick and R. L. Robertson, Fr. Demande 2,132,378 (1972) [CA 78, 159673 (1973)].

cultures of *Streptomyces aureus*, have been shown by degradative study to contain a quinoxaline-2-carboxylic acid residue. A recent ^{13}C nuclear magnetic resonance (NMR) and mass spectrometric study of quinomycin A (echinomycin) (1) has led to revised structures for the quinomycins, which were originally thought to be cross-linked with a dithian rather than a thioacetal unit.⁶



In recent years, unusual quinoxaline derivatives such as 1,3-ethano-1,2,3,4-tetrahydroquinoxaline (2)⁷ have been prepared, together with many condensed quinoxalines. Fusion to the 1,2-bond is illustrated by the formation of triazoloquinoxalium salts, such as compound 3,⁸ and numerous examples of condensed systems resulting from fusion to the 2,3-bond are to be found in the subsequent text. An interesting pentacyclic derivative, methylquinoxaline orange (4), is obtained on oxidation of 2-methylquinoxaline.⁹ The numbering of the quinoxaline ring system is shown in structure 5; the 2- and 3-positions are also designated as α -positions.

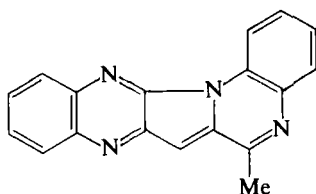


⁶ (a) H. Otsuka and J. Shoji, *J. Antibiot., Ser. A* **16**, 52 (1963) [*CA* **60**, 4250 (1964)]; (b) **19**, 128 (1966) [*CA* **66**, 5574 (1967)]; (c) *Tetrahedron* **23**, 1535 (1967); (d) A. Dell, D. H. Williams, H. R. Morris, G. A. Smith, J. Feeney, and G. C. K. Roberts, *J. Am. Chem. Soc.* **97**, 2497 (1975).

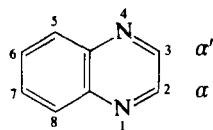
⁷ H. C. Cunningham and A. R. Day, *J. Org. Chem.* **38**, 1225 (1973).

⁸ A. Messmer and O. Sziman, *Angew. Chem., Int. Ed. Engl.* **4**, 1074 (1965).

⁹ G. W. H. Cheeseman and B. Tuck, *Tetrahedron Lett.*, 4851 (1968).



(4)

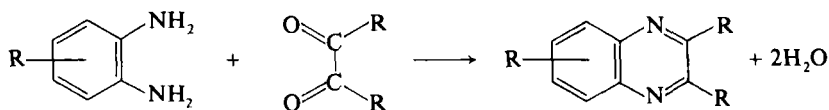


(5)

II. Synthesis

A. PREPARATION OF QUINOXALINES FROM *o*-DIAMINES

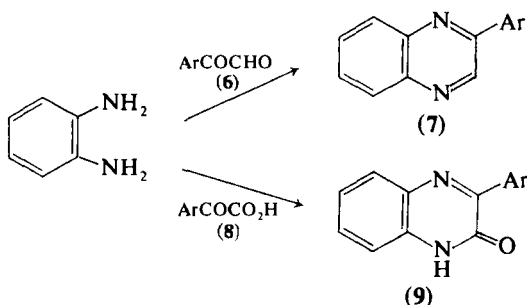
The classical synthesis of quinoxalines involves the condensation of an aromatic *o*-diamine and an α -dicarbonyl compound (Scheme 1).



SCHEME 1

The reaction is facile, and it is still the most widely used for the synthesis of both quinoxaline itself and many of its substituted derivatives. The condensation of glyoxal with *o*-phenylenediamine, followed by sodium carbonate addition, yields quinoxaline in almost quantitative yield.¹⁰

Substituted phenylglyoxals (**6**) are the starting α -dicarbonyl compounds for the synthesis of 2-arylquinoxalines (**7**),¹¹ and the corresponding aryl α -ketoacids (**8**) yield 3-aryl-2-quinoxalinones (**9**).^{11,12}

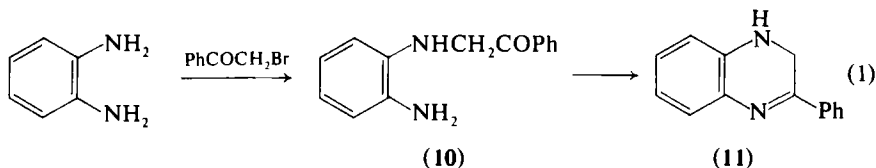


¹⁰ (a) A. Zmojdzin and B. Hoffmann, Ger. Offen. 2,326,784 (1973) [CA **80**, 59962 (1974)]; (b) A. Zmojdzin, Pol. Patent 69,644 (1974) [CA **81**, 77966 (1974)].

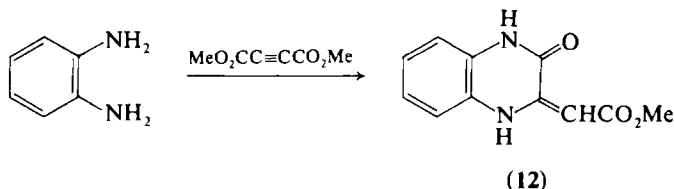
¹¹ D. Nardini, A. Tajana, and E. Masserani, *Ann. Chim. (Rome)* **59**, 1075 (1969).

¹² R. Pohloudek-Fabini and E. Papke, *Pharmazie* **18**, 273 (1963).

The kinetics of the reaction between *o*-phenylenediamine and phenacyl bromide has been investigated and found to be a two-step process (Eq. 1). The intermediate **10** cyclized to give the dihydrophenylquinoxaline (**11**). The first stage is characterized by second-order kinetics and has an activation energy of 9.70 kcal/mole; the second stage has an activation energy of 12.5 kcal/mole.¹³



The reaction of dimethyl acetylenedicarboxylate with *o*-phenylenediamines yields 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines, e.g., **12**.^{14–16}



$\beta\gamma$ -Acetylenic- α -ketoacid esters also condense with *o*-phenylenediamine¹⁷; under nonaqueous conditions the quinoxalinone **14** was obtained (68%) from ethyl phenylethynylglyoxylate (**13**); however, in the presence of aqueous base, 2-phenacyl-3-quinoxalinone (**15**) (83%) was isolated.

Ethyl- α -chlorophenylacetate and *o*-phenylenediamine in the presence of triethylamine give 3-phenyl-1,2,3,4-tetrahydro-2-quinoxalinone (**16**), which is oxidized to 3-phenyl-2-quinoxalinone (**17**) with potassium

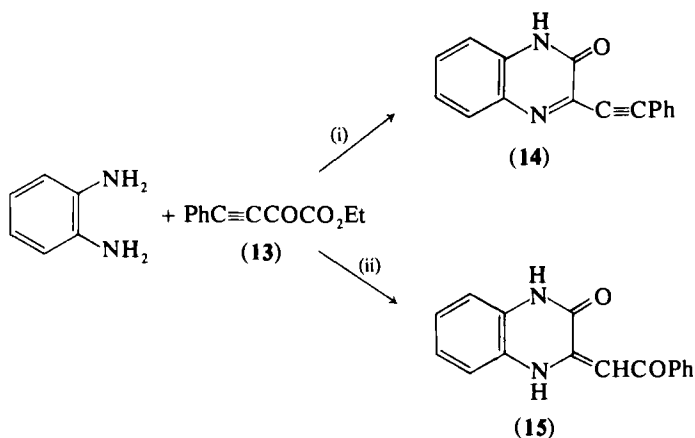
¹³ D. M. Aleksandrova, L. I. Kolotova, and L. Ya. Kheifets, *Zh. Org. Khim.* **9**, 2107 (1973) [*CA* **80**, 36469 (1974)].

¹⁴ (a) Y. Iwanami, *Nippon Kagaku Zasshi* **82**, 778 (1961) [*CA* **58**, 11354 (1963)]; (b) **83**, 593 (1962) [*CA* **59**, 5153 (1963)]; (c) N. D. Heindel, T. F. Lemke, H. R. Harless, and L. E. Brydia, *Proc. West Va. Acad. Sci.* **38**, 250 (1966) [*CA* **68**, 59552 (1968)]; (d) Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 316 (1962) [*CA* **59**, 3939 (1963)].

¹⁵ L. I. Vereshchagin, L. D. Gavrilov, R. L. Bolshedvorskaya, E. I. Titova, S. R. Buzilova, A. V. Maksikova, and G. A. Kalabin, *Zh. Org. Khim.* **10**, 2059 (1974) [*CA* **82**, 43338 (1975)].

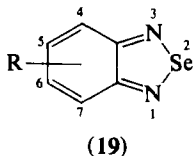
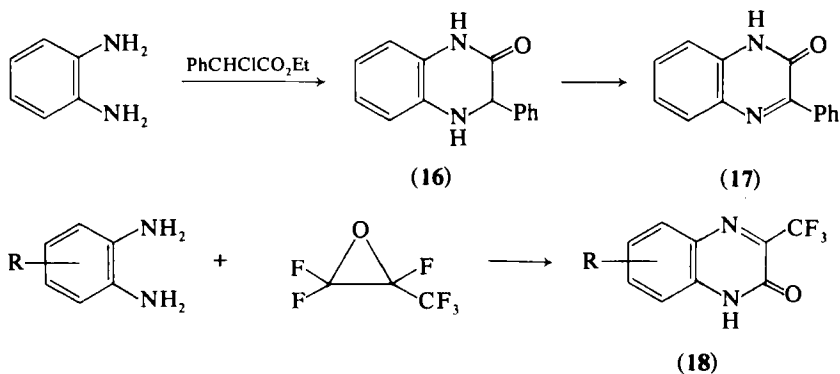
¹⁶ H. Suschitzky, B. J. Wakefield, and R. A. Whittaker, *J. Chem. Soc., Perkin Trans. I*, 401 (1975).

¹⁷ Yu. S. Andreichikov and R. F. Saraeva, *Khim. Geterotsikl. Soedin.*, 705 (1973) [*CA* **79**, 42449 (1973)].



(i) Ether (ii) 10% Aqueous-ethanolic alkali

permanganate or selenious acid (H₂SeO₃) in acetic acid.¹⁸ 3-Trifluoromethyl-2-quinoxalinones (18) have been obtained from hexafluoropropylene oxide and arylenediamines,¹⁹ and 2,3-bis(trifluoromethyl)quinoxaline from perfluorobiacetyl and *o*-phenylenediamine.²⁰



¹⁸ (a) H. Zellner, Ger. Offen. 1,804,328 (1969) [CA 71, 70642 (1969)]; (b) Donnan-Pharmazie G.m.b.H., Austrian Patent 284,848 (1970) [CA 74, 64258 (1971)].

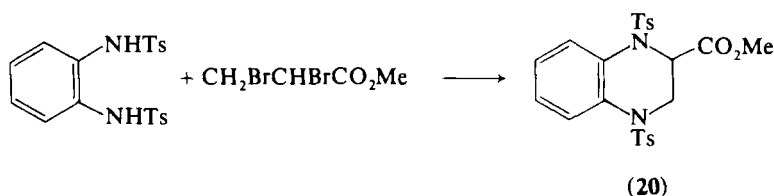
¹⁹ J. E. Nottke, U.S. Patent 3,928,350 (1975) [CA 84, 105652 (1976)].

²⁰ L. O. Moore and J. W. Clark, *J. Org. Chem.* 30, 2472 (1965).

The preparation of quinoxaline derivatives carrying a substituent in the benzene ring requires suitably substituted *o*-phenylenediamines. These have been prepared by reductive cleavage (SnCl_2) of appropriately substituted 2,1,3-benzoselenadiazoles (19).²¹ Benzoselenadiazoles, readily prepared from 1,2-diaminobenzenes and selenium dioxide, undergo halogenation at positions 4 and 7 and sulfonation at C-4. 5,6-Dichloro- 2,3-diphenylquinoxaline has been synthesized from benzil and 1,2-diamino-3,4-dichlorobenzene, the diamine in turn was obtained from 4,5-dichloro-2,1,3-benzoselenadiazole.²²

Benzotriazoles can also be cleaved reductively to give the corresponding substituted 1,2-diaminobenzenes.²³ For example, 1,2-diamino-3,4,5,6-tetrachlorobenzene, formed by cleavage of the corresponding triazole with zinc and hydrochloric acid, on condensation with glyoxal yielded 5,6,7,8-tetrachloroquinoxaline,²⁴ which has fungicidal activity.

N-Substituted quinoxalines are obtained from N-substituted *o*-phenylenediamines. Thus methyl 2,3-dibromopropionate condenses with *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine to give 1,4-bis(*p*-toluenesulfonyl)-2-methoxycarbonyl-1,2,3,4-tetrahydroquinoxaline (20).²⁵ *N,N'*-Disubstituted cyclohexane-1,2-diamines with suitable $\alpha\beta$ -dihalides yield decahydroquinoxalines.²⁶ Condensation of cyclohexane-1,2-diones with glycine amide gives 2-oxo-5,6,7,8-tetrahydroquinoxalines.²⁷



The unusual condensation between alloxan and *o*-amino-*N,N*-dimethylaniline yields the tetrahydroquinoxaline spiran 21.²⁸ A possible mechanism for spiran formation involves the acid-promoted cyclization

²¹ C. W. Bird, G. W. H. Cheeseman, and A. A. Sarsfield, *J. Chem. Soc.*, 4767 (1963).

²² G. W. H. Cheeseman and E. S. G. Torzs, *J. Chem. Soc. C*, 157 (1966).

²³ D. E. Burton, A. J. Lambie, D. W. J. Lane, G. T. Newbold, and A. Percival, *J. Chem. Soc. C*, 1268 (1968).

²⁴ Fisons Pest Control Ltd., Belg. Patent 631,044 (1963) [CA 60, 15891 (1964)].

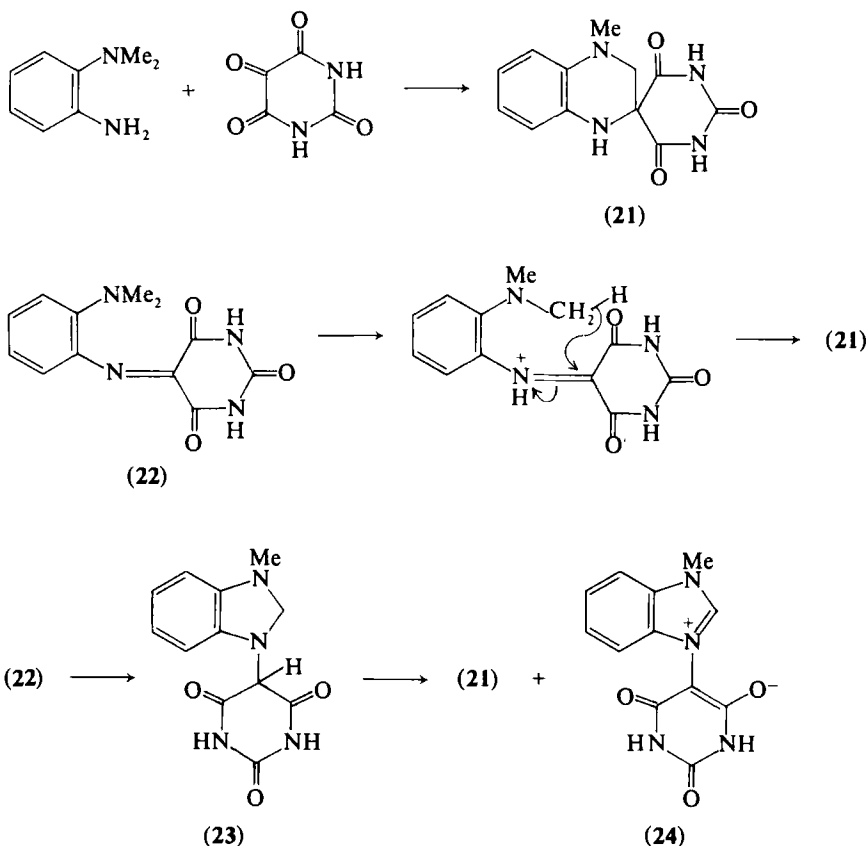
²⁵ G. H. Fisher and H. P. Schultz, *J. Org. Chem.* 39, 631 (1974).

²⁶ S. I. Burmistrov, N. V. Makarevich, and L. Ya. Kravchenko, U.S.S.R. Patent 390,091 (1973) [CA 79, 126527 (1973)].

²⁷ B. Miller and T. H. Mladineo, U.S. Patent 3,505,327 (1970) [CA 72, 132785 (1970)].

²⁸ J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Aust. J. Chem.* 17, 877 (1964).

of the intermediate anil **22**.²⁹ However, later work suggests that the quinoxaline spiran is probably formed through an intermediate dihydrobenzimidazole (**23**), which subsequently undergoes acid-catalyzed ring expansion to the spiroquinoxaline **21**. Alternatively, oxidation of the dihydrobenzimidazole gives the betaine **24**.^{30,31}



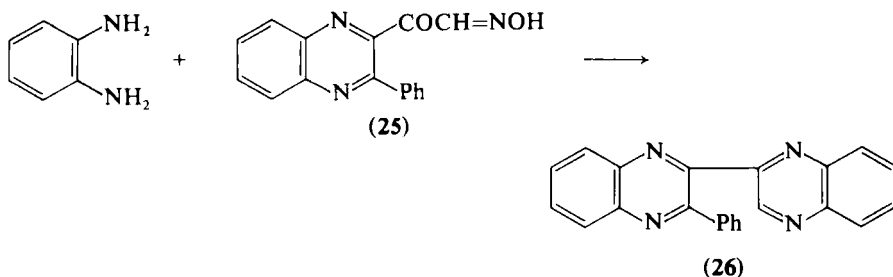
A further extension of the classical reaction sequence for quinoxaline synthesis involves the use of alicyclic or heterocyclic α -dicarbonyl compounds or their derivatives. The quinoxalinyglyoxal oxime **25** thus yields the 2,2'-bisquinoxaline **26**.³²

²⁹ J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Aust. J. Chem.* **18**, 907 (1965).

³⁰ J. W. Clark-Lewis, K. Moody, and M. J. Thompson, *Aust. J. Chem.* **23**, 1249 (1970).

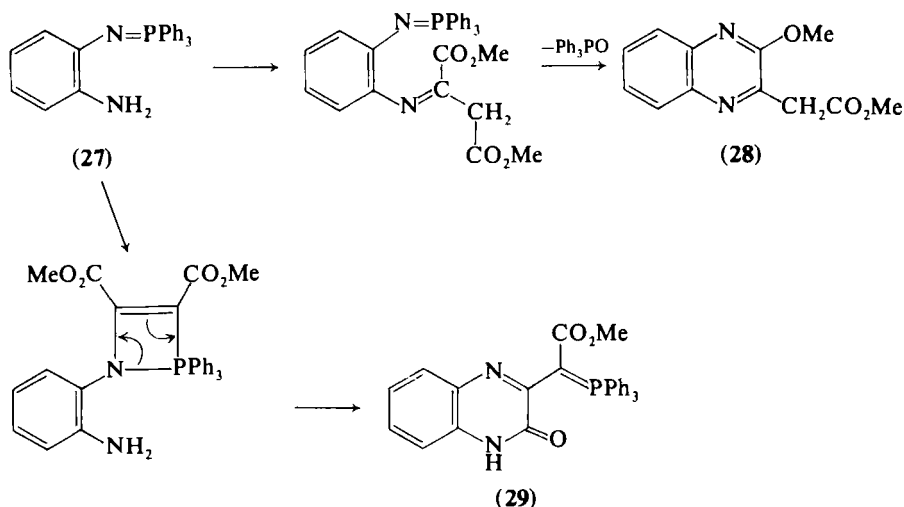
³¹ R. K. Grantham, O. Meth-Cohn, and M. A. Naqui, *J. Chem. Soc. C*, 1438 (1969).

³² V. V. Titov and L. F. Kozhokina, *Khim. Geterotsikl. Soedin.*, 1289 (1972) [*CA* **78**, 4217 (1973)].



2-Bromocyclobutanone and *o*-phenylenediamine condense to give the strained ring system cyclobuta[*b*]quinoxaline,³³ and the cyclopenta[*b*]quinoxaline ring system is similarly synthesized from suitable cyclopentanedione derivatives.³⁴

Reaction of the iminotriphenylphosphorane **27** with dimethyl acetylenedicarboxylate gives a mixture of the quinoxalines **28** and **29**. The formation of compound **28** can be rationalized as shown, ring closure involving Wittig-like elimination of triphenylphosphine oxide. The formation of compound **29** is thought to involve a phosphazacyclobutene intermediate.³⁵



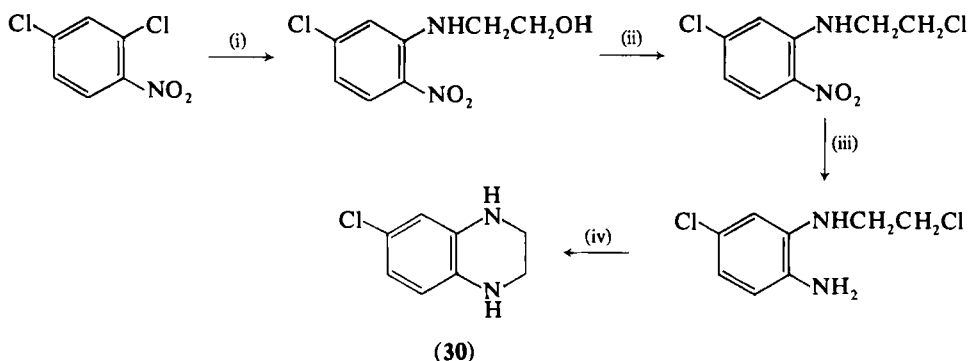
³³ J. H. Markgraf, W. P. Homa, R. J. Katt, and W. L. Scott, *J. Heterocycl. Chem.* **6**, 135 (1969).

³⁴ (a) Y. Suzuki, M. Sawai, Y. Hosoyama, and O. Kobayashi, Japanese Patent 11,748 (1967) [*CA* **68**, 78312 (1968)]; (b) G. R. Wendt and K. W. Ledig, U.S. Patent 3,376,284 (1968) [*CA* **69**, 52181 (1968)]; (c) U.S. Patent 3,361,747 (1968) [*CA* **69**, 36178 (1968)].

³⁵ E. M. Briggs, G. W. Brown, W. T. Dawson, and J. Jiricny, *Chem. Commun.*, 641 (1975).

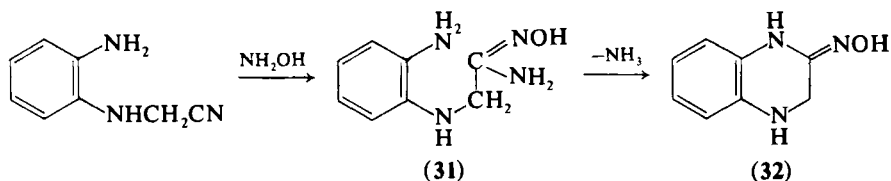
B. PREPARATION OF QUINOXALINES BY INTRAMOLECULAR CYCLIZATION REACTIONS

6-Chloro-1,2,3,4-tetrahydroquinoxaline (**30**) has been synthesized in 52% yield by cyclizing the corresponding *o*-(*N*-2'-chloroethylamino)-aniline, which in turn was obtained from 2,4-dichloronitrobenzene via the sequence shown in Scheme 2.³⁶ The amidoxime **31**, prepared from *N*-cyanomethyl-*o*-phenylenediamine and hydroxylamine, cyclizes to 2-(hydroxyimino)-1,2,3,4-tetrahydroquinoxaline (**32**).³⁷



Reagents: (i) $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$, (ii) SOCl_2 , (iii) $\text{H}_2/\text{Raney Ni}$, (iv) Reflux in EtOH

SCHEME 2



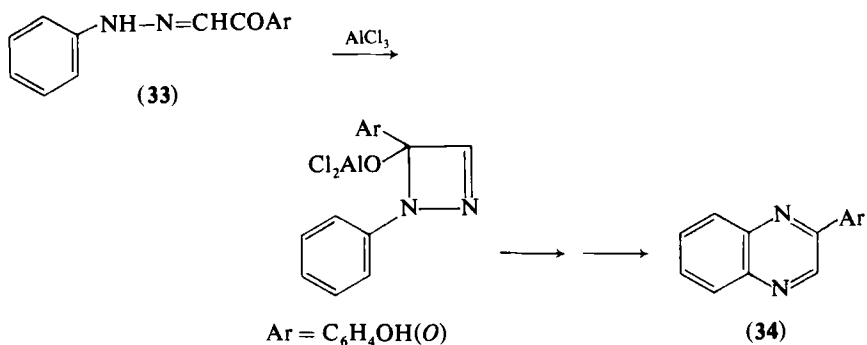
Cyclodehydration of *cis*-phenylglyoxal-2-phenylhydrazone with anhydrous $\text{AlCl}_3\text{-NaCl}$, at $150^\circ\text{--}160^\circ$ yields some 2-phenylquinoxaline, together with 4-phenylcinnoline.³⁸ The same workers prepared 2-(*o*-hydroxyphenyl)quinoxaline (**34**) from *o*-hydroxyphenylglyoxal-2-phenylhydrazone (**33**) under similar conditions. Quinoxaline formation is thought to proceed through a diazetine intermediate as shown.³⁹

³⁶ P. Clarke and A. Moorhouse, *J. Chem. Soc.*, 4763 (1963).

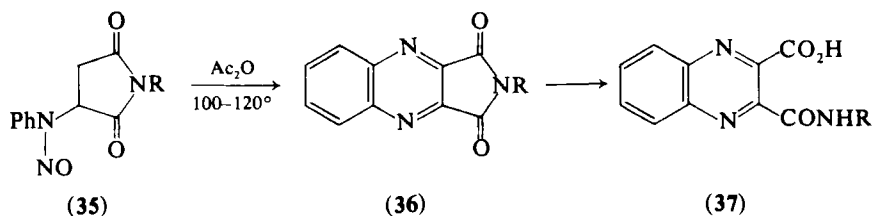
³⁷ K. Harsanyi, C. Goncz, G. Horvath, and D. K. Korbonits, *Chem. Ber.* **105**, 805 (1972).

³⁸ S. N. Bannore and J. L. Bose, *Indian J. Chem.* **11**, 631 (1973).

³⁹ S. N. Bannore, V. V. Bhat, and J. L. Bose, *Indian J. Chem.* **12**, 139 (1974).

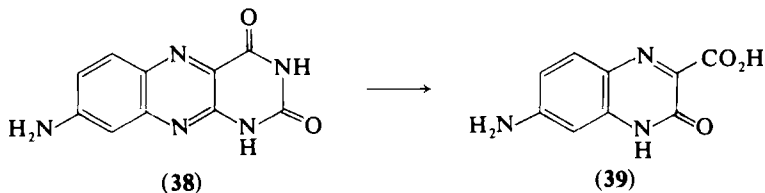


Quinoxaline derivatives (36), and not the expected sydnones, were obtained from the *N*-nitroso derivatives of 3-arylamino-1-arylpyrrolidine-2,5-diones (35). The precise nature of this rearrangement has not so far been determined.⁴⁰ The derived quinoxaline-2,3-dicarboxylic acid mono-*N*-arylamides (37) were obtained in 40–60% yield. The latter compounds were also made by the conventional reaction of quinoxaline 2,3-dicarboxylic anhydride and an amine.⁴⁰



C. PREPARATION OF QUINOXALINES FROM ALLOXAZINES, DIAZEPINES, AND QUINONE DIIMIDES

1,2-Dihydro-2-oxoquinoxalinecarboxylic acids are isolated from alkaline hydrolysis of fused alloxazines. Thus the alloxazine 38 with 2*N* NaOH (150°, 24 hours) yields the 7-aminoquinoxalinone derivative 39.⁴¹

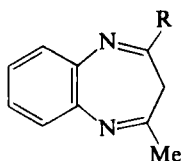


⁴⁰ S. I. Burmistrov, N. E. Kul'chitskaya, and V. D. Romaneko, *Zh. Org. Khim.* **8**, 1095 (1972) [*CA* **77**, 61947 (1972)].

⁴¹ V. M. Berezovskii, N. A. Polyakova, and L. S. Tul'chinskaya, *Khim. Geterotsikl. Soedin.*, 729 (1967) [*CA* **68**, 78254 (1968)].

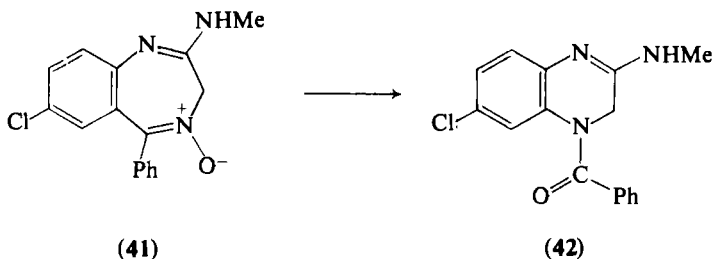
The 1,5-benzodiazepine **40** on irradiation in benzene under oxygen undergoes oxidative ring contraction to 2-benzoyl-3-methylquinoxaline.⁴² Similarly, photolysis of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide (**41**) in benzene yields the *N*-benzoylquinoxaline **42**. Related ring contractions of diazepines to reduced quinoxalines have also been observed.⁴³

The dimethyl-1,5-benzodiazepine **43** on attempted nitration with $\text{H}_2\text{SO}_4\text{-HNO}_3$ at $0^\circ\text{--}5^\circ$ gave, by ring contraction, 2-acetyl-3-methylquinoxaline (26%), together with some of the *N,N'*-diacetyl derivative of 1,2-diamino-4-nitrobenzene.⁴⁴



(**40**) $\text{R} = \text{Ph}$

(**43**) $\text{R} = \text{Me}$



(**41**)

(**42**)

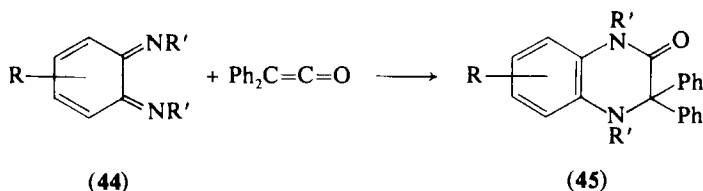
Cycloaddition of diphenyl ketene with benzoquinone diimides (**44**) gives quinoxalinones of type **45**.⁴⁵ Analogous additions of olefins lead to tetrahydroquinoxalines; these reactions are classified as Diels–Alder additions with inverse electronic demand.

⁴² M. Matsumoto, Y. Matsumura, A. Iio, and T. Yonezawa, *Bull. Chem. Soc. Jpn.* **43**, 1496 (1970).

⁴³ (a) R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.* **7**, 475 (1970); (b) A. Walser, G. Silverman, R. I. Fryer, and L. H. Sternbach, *J. Org. Chem.* **36**, 1248 (1971); (c) G. F. Field and L. H. Sternbach, U.S. Patent 3,555,022 (1971) [*CA* **75**, 5980 (1971)]; (d) U.S. Patent 3,697,545 (1972) [*CA* **78**, 16253 (1973)]; (e) T. Yonezawa, M. Matsumoto, and H. Kato, *Bull. Chem. Soc. Jpn.* **41**, 2543 (1968).

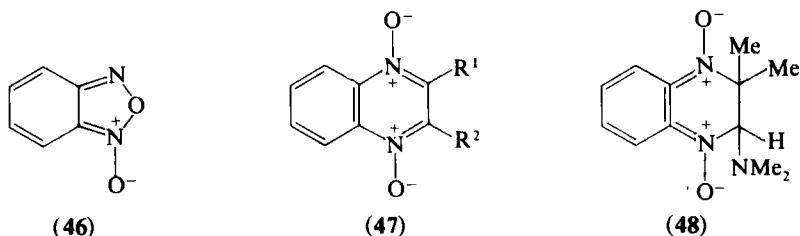
⁴⁴ K. V. Levshina, L. P. Glazyrina, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, 1133 (1970) [*CA* **74**, 31726 (1971)].

⁴⁵ W. Friedrichsen, *Angew. Chem., Int. Ed. Engl.* **13**, 348 (1974).



D. PREPARATION OF QUINOXALINE *N*-OXIDES FROM BENZOFURAZAN 1-OXIDES AND *o*-QUINONE DIOXIMES

Haddadin and Issidorides first reported an elegant method for the synthesis of quinoxaline 1,4-dioxides (47) from the reaction of benzofurazan 1-oxide (46) and an enamine or an active methylene compound, such as a β -diketone or a β -ketoester, in the presence of base.^{46,47} Quinoxaline 1,4-dioxide formation formally involves loss of secondary amine in the enamine reaction and loss of water when an active methylene compound of the type $\text{R}^1\text{CH}_2\text{COR}^2$ is used. This reaction is now commonly referred to as the Beirut reaction. The isolation of the dihydroquinoxaline 1,4-dioxide 48 from the reaction of 46 and *N,N*-dimethylisobutenylamine ($\text{Me}_2\text{C}=\text{CHNMe}_2$), which is unable to aromatize by amine loss, suggests that 2,3-dihydroquinoxalines are likely intermediates in all these reactions.⁴⁸



Work from several laboratories has demonstrated the utility of this method.⁴⁹⁻⁵² In addition to enamines and 1,3-dicarbonyl compounds,⁴⁹

⁴⁶ (a) C. H. Issidorides and M. J. Haddadin, *Tetrahedron Lett.*, 3253 (1965); (b) M. J. Haddadin and C. H. Issidorides, U.S. Patent 3,398,141 (1968) [*CA* **69**, 10650 (1968)].

⁴⁷ (a) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.* **31**, 4067 (1966); (b) British Patent 1,215,815 (1970) [*CA* **74**, 141873 (1971)].

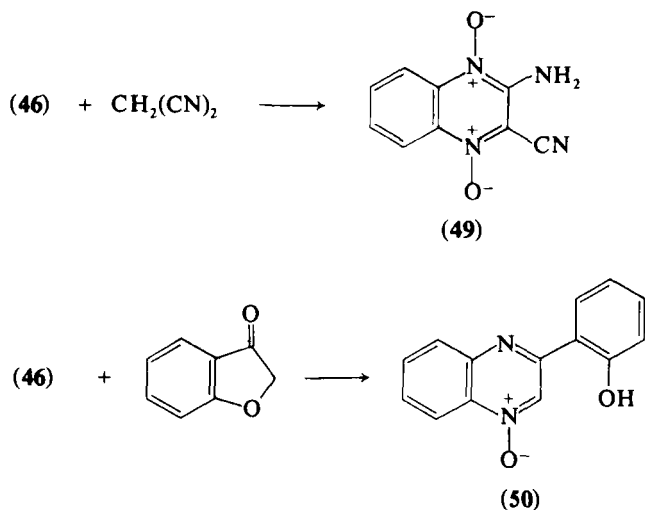
⁴⁸ J. W. McFarland, *J. Org. Chem.* **36**, 1842 (1971).

⁴⁹ (a) N. A. Mufarrij, M. J. Haddadin, C. H. Issidorides, J. W. McFarland, and J. D. Johnston, *J. Chem. Soc. Perkin Trans. 1*, 965 (1972); (b) M. J. Haddadin, N. C. Chelhot, and M. Pieridou, *J. Org. Chem.* **39**, 3278 (1974).

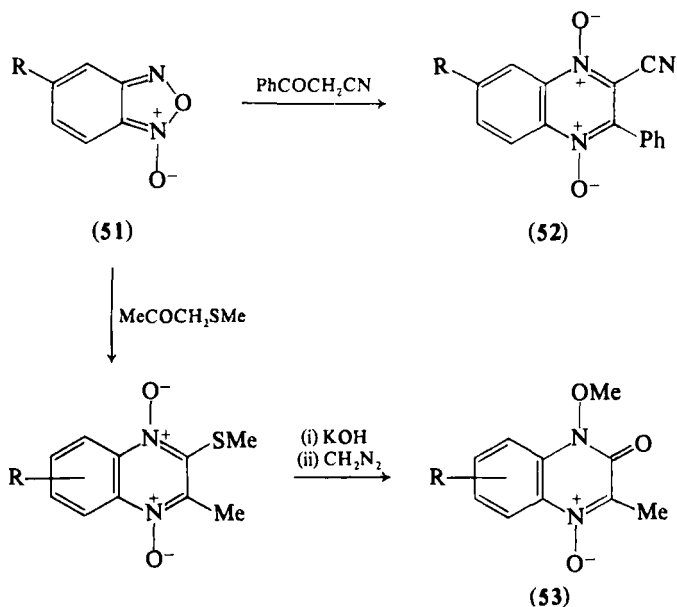
⁵⁰ K. Ley, F. Seng, U. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.* **8**, 596 (1968).

⁵¹ J. J. Zamet, M. J. Haddadin, and C. H. Issidorides, *J. Chem. Soc. Perkin Trans. 1*, 1687 (1974).

⁵² E. Abushanab and N. D. Alteri, *J. Org. Chem.* **40**, 157 (1975).



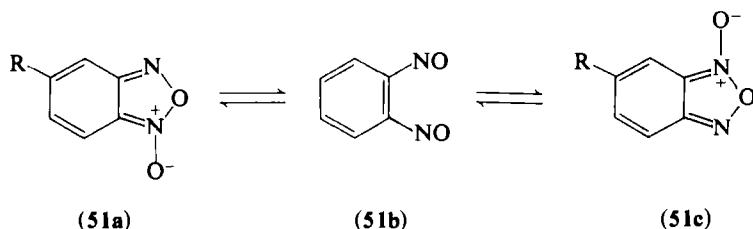
simple carbonyl compounds condense with benzofurazan 1-oxide⁵⁰; e.g., methyl ethyl ketone gives 2,3-dimethylquinoxaline 1,4-dioxide in excellent yield. Malononitrile gives the dioxide **49**.⁵⁰ Benzofuran-3(2*H*)-ones yield 3-(*o*-hydroxyphenyl)quinoxaline 1-oxides (**50**), involving reduction by the furanone.⁵¹



R = 6- or 7-Me, OMe, or CO₂Me

Mixtures of isomeric di-*N*-oxides are generally obtained when 5(6)-substituted benzofurazan 1-oxides (**51**) are used in the Beirut reaction^{52–54}; however, only 7-substituted 2-cyano-3-phenylquinoxaline 1,4-dioxides (**52**) were isolated from benzoylacetonitrile (PhCOCH_2CN).⁵⁵ The di-*N*-oxide mixtures obtained from reaction with acetonyl methyl sulfide ($\text{MeCOCH}_2\text{SMe}$) were analyzed by ^1H nuclear magnetic resonance (NMR) analysis of the mixed hydroxamic esters (**53**) formed by hydrolysis and methylation of the primary products.⁵²

From the variation in the ratios of 6- and 7-hydroxamic esters formed in the last reaction, it was concluded that benzofurazan 1-oxides react in their *o*-dinitrosobenzene form **51b**, which are intermediate between the rapidly interconverting tautomers **51a** and **51c**.



A further variation on this general method for preparing quinoxaline dioxides is the use of *o*-quinone dioximes (**54**) rather than benzofurazan 1-oxides. The dioxime undergoes cycloaddition with α -dicarbonyl and α -hydroxycarbonyl compounds, and hydroxamic acids of type **55** are particularly easily prepared by this method.⁵⁶

There are many patents on the Beirut reaction; thus 2-carbamoyl,⁵⁷ 2-amino-3-amidino,⁵⁸ 2-methyl-3-carbamoyl,⁵⁹ 2-amino-3-carbamoyl,⁶⁰ 2-halomethyl-3-carboxy,⁶¹ 2-mercapto-,⁶² and 2-trifluoromethyl⁶³ quinoxaline 1,4-dioxides are just a few examples among the many quinoxaline derivatives prepared by this method. In a

⁵³ M. J. Haddadin, G. Agopian, and C. H. Issidorides, *J. Org. Chem.* **36**, 514 (1971).

⁵⁴ W. Duerckheimer, *Justus Liebigs Ann. Chem.* **756**, 145 (1972).

⁵⁵ G. Tennant and J. C. Mason, *Chem. Commun.*, 586 (1971).

⁵⁶ (a) E. Abushanab, *J. Org. Chem.* **35**, 4279 (1970); (b) Ger. Offen. 1,929,541 (1968) [*CA* **72**, 66981 (1970)].

⁵⁷ E. H. Abu and J. Marwan, Ger. Offen. 2,316,765 (1973) [*CA* **80**, 27291 (1974)].

⁵⁸ F. Seng, K. Ley, K. G. Metzger, and D. Fritsche, S. African Patent 68 04,947 [*CA* **71**, 101888 (1969)].

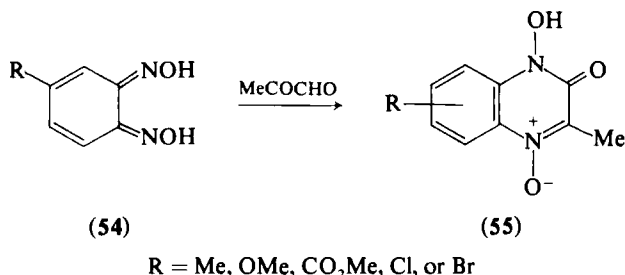
⁵⁹ Farbenfabriken Bayer A.-G., Fr.M. 8123 (1970) [*CA* **76**, 153774 (1972)].

⁶⁰ F. Seng, K. Ley, K. G. Metzger, and D. Fritsche, British Patent 1,174,874 (1969) [*CA* **72**, 66984 (1970)].

⁶¹ Pfizer Inc., British Patent (Amended) 1,303,372 (1973) [*CA* **81**, 63674 (1974)].

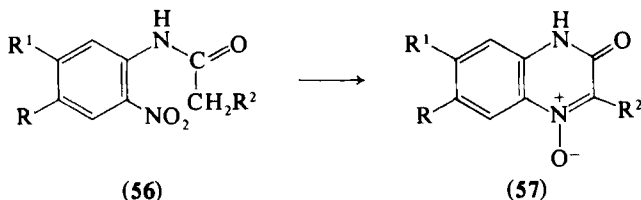
⁶² F. Seng and K. Ley, Ger. Offen. 2,338,722 [*CA* **83**, 10148 (1975)].

⁶³ E. Abushanab, Ger. Offen. 2,105,112 (1971) [*CA* **75**, 110336 (1971)].



unique case of *mono-N*-oxide formation from benzofurazan 1-oxide, 2,3-bisethoxycarbonylquinoxaline 1-oxide results from reaction with ethyl oxaloacetate (EtO₂CCOCH₂CO₂Et).⁶⁴ A recent review of the application of benzofurazan 1-oxides in the synthesis of heteroaromatic *N*-oxides provides a valuable summary of the literature.⁶⁵

Cyclization of α -aryl-*o*-nitroacetanilides **56** to quinoxaline *N*-oxides has been reported independently by three groups.⁶⁶⁻⁶⁸ Thus treatment with ethanolic sodium ethoxide of **56** (R=R¹=H; R²=Ph), synthesized from *o*-nitroaniline and PhCH₂COCl, gives 1,2-dihydro-2-oxo-3-phenylquinoxaline 4-oxide (**57**; R=R¹=H, R²=Ph).



III. General Reactions

A. NUCLEAR SUBSTITUTION

1. Electrophilic and Free-Radical Substitution Reactions

Sulfonation of quinoxaline-2,3-dione (**58**) with fuming sulfuric acid yields the 6-sulfonic acid (**59**).⁶⁹ Similarly, if quinoxaline-2,3-dione is

⁶⁴ M. L. Edwards, R. E. Bambury, and H. W. Ritter, *J. Med. Chem.* **19**, 330 (1976).

⁶⁵ M. J. Haddadin and C. H. Issidorides, *Heterocycles* **4**, 767 (1976).

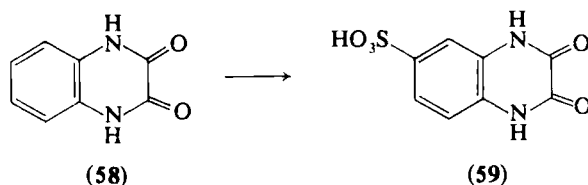
⁶⁶ (a) Y. Ahmad, M. S. Habib, and Ziauddin, *Tetrahedron* **20**, 1107 (1964); (b) Y. Ahmad, M. S. Habib, Ziauddin, and Naz Bashir, *ibid.* **21**, 861 (1965).

⁶⁷ (a) R. Fusco and S. Rossi, *Gazzetta* **94**, 3 (1964); (b) R. Fusco and S. Rossi, *Chim. Ind., (Milan)* **45**, 834 (1963).

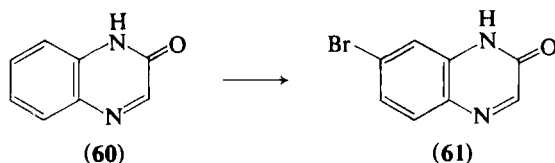
⁶⁸ (a) G. Tennant, *J. Chem. Soc.*, 2428 (1963); (b) 2666 (1964); (c) C, 2285 (1966).

⁶⁹ (a) Sumitomo Chemical Co. Ltd., Belgian Patent 635,579 (1963) [*CA* **61**, 15288 (1964)]; (b) Sumitomo Chemical Co. Ltd., Netherlands Appl. 295,925 (1964) [*CA* **62**, 1032 (1965)]; (c) Sumitomo Chemical Co. Ltd. (by J. Hattori, S. Koike, T. Ozaki, K. Yoshioka, and H. Sugiyama), British Patent 1,043,042 (1966) [*CA* **65**, 20778 (1966)].

treated with chlorosulfonic acid at elevated temperatures, the 6-sulfonyl chloride is obtained. 6-Methylquinoxaline-2,3-dione under these conditions yields the 7-sulfonyl chloride, and the 5-methyl derivative is reported to give the 6- and 7-substituted products.⁷⁰ Reaction of 2,3-dimethylquinoxaline with 20% HNO_3 at 90° for 15 hours gives a mixture of 6-nitro- and 6,7-dinitroquinoxaline-2,3-dione, presumably as a result of intermediate formation of quinoxaline-2,3-dione.⁷¹



Halogenation of 2-quinoxalinone (60) in acetic acid gives the 7-substituted product almost quantitatively: bromine at 20° thus yields 95% of 7-bromo-2-quinoxalinone (61).⁷²



2-Benzylquinoxaline (62) is the only product isolated from the homolytic benzylation of quinoxaline with dibenzyl mercury.⁷³ Gardini and Minisci found that homolytic alkylation,⁷⁴ acylation,⁷⁵ α -oxyalkylation,⁷⁶ carboxylation,⁷⁷ and δ -aminoalkylation⁷⁸ of quinoxaline always gave the 2-substituted product. When a mixture of quinoxaline and ferrous sulfate is treated with *N*-chlorodi-*n*-butylamine, exclusive 2-substitution occurs in 50% sulfuric acid, but in concentrated acid a

⁷⁰ Sumitomo Chemical Co. Ltd. (by H. Sugiyama, T. Ikeda, and S. Koike), Japanese Patent 26,975 (1964) [CA 62, 11833 (1965)].

⁷¹ A. S. Elina, L. G. Tsyrlnikova, and M. I. Medvedeva, *Zh. Org. Khim.* 1, 147 (1965) [CA 62, 14673 (1965)].

⁷² P. Linda and G. Marino, *Ric. Sci., Rend. Ser. A.* 3, 225 (1963) [CA 59, 7523 (1963)].

⁷³ K. C. Bass and P. Nababsing, *Org. Prep. Proc. Int.* 3, 45 (1971) [CA 74, 99988 (1971)].

⁷⁴ G. P. Gardini and F. Minisci, *Ann. Chim. (Rome)* 60, 746 (1970).

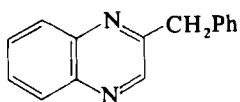
⁷⁵ T. Caronna, G. P. Gardini, and F. Minisci, *Chem. Commun.*, 201 (1969).

⁷⁶ W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron* 27, 3655 (1971).

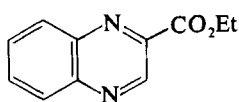
⁷⁷ R. Bernardi, T. Caronna, R. Galli, F. Minisci, and M. Perchinunno, *Tetrahedron Lett.*, 645 (1973).

⁷⁸ A. Citterio, M. Ghirardini, and F. Minisci, *Tetrahedron Lett.*, 203 (1976).

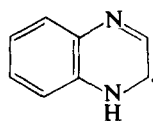
mixture of 2- and 6-(4-*n*-butylaminobutyl)quinoxaline is obtained. Abnormal substitution at position 6 is explained by postulating radical attack on the diprotonated species.⁷⁸ The radicals are generated under oxidizing conditions with hydrogen peroxide, or *t*-butylhydroperoxide and ferrous sulfate. Thus 2-ethoxycarbonylquinoxaline (**63**) is obtained in good yield from quinoxaline and the ethylpyruvate-hydrogen peroxide adduct [$\text{CH}_3\text{C}(\text{OH})(\text{OOH})\text{CO}_2\text{Et}$]. The latter is decomposed in the presence of aqueous ferrous sulfate generating EtO_2C radicals.⁷⁷ Quinoxaline and formamide, in the presence of 30% hydrogen peroxide, sulfuric acid, and ferrous sulfate at $10^\circ\text{--}15^\circ$, give 2-quinoxaline carboxamide (95%)⁷⁹ 2-Quinoxaline carboxaldehyde and quinoxalin-2-yl ketones have also been obtained via homolytic acylation.⁸⁰ Recently, it has also been reported⁸¹ that substitution of quinoxaline takes place at C-2 when it is irradiated in ether, MeOH, or EtOH. The intermediate in the reaction is the quinoxaline radical **64**.



(62)

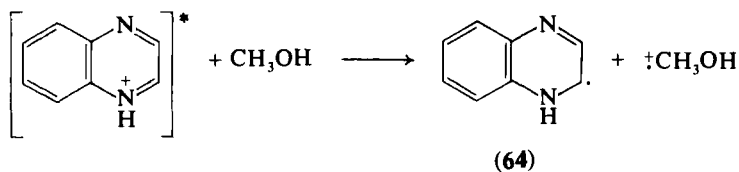


(63)



(64)

The UV irradiation of quinoxaline in methanol yields radicals, not by hydrogen abstraction, but by protonation of the first singlet excited state, followed by exiplex formation.⁸² Irradiation of quinoxaline in acidified methanol furnishes 2-methylquinoxaline, and the reaction is suggested to go through a pathway involving electron-transfer from the solvent to an excited state of the protonated quinoxaline (Scheme 3).⁸³



(64)

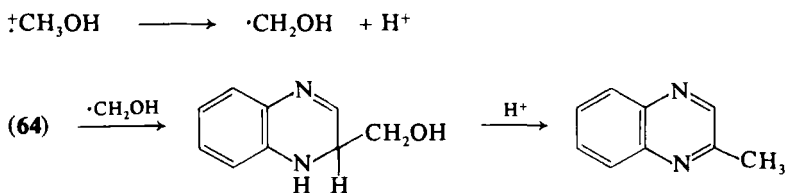
⁷⁹ F. Minisci, R. Galli, and A. Quilico, Ger. Offen. 2,056,433(1971) [*CA* **75**, 49055 (1971)].

⁸⁰ (a) G. P. Gardini and F. Minisci, *J. Chem. Soc. C*, 929 (1970); (b) *Tetrahedron Lett.*, 4113 (1972).

⁸¹ A. Castellano, J. P. Catteau, A. Lablache-Combier, B. Planckaert, and G. Allen, *Tetrahedron* **28**, 3511 (1972).

⁸² A. Castellano, J. P. Catteau, and A. Lablache-Combier, *Chem. Commun.*, 1207 (1972).

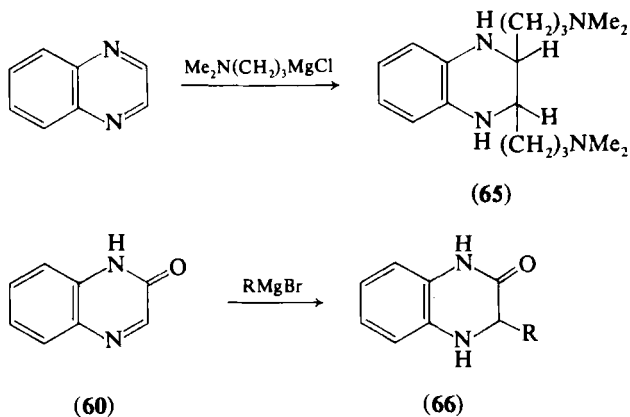
⁸³ S. Wake, Y. Takayama, Y. Otsuji, and E. Imoto, *Bull. Chem. Soc. Jpn.* **47**, 1257 (1974).



SCHEME 3

2. Nucleophilic Reactions

As stated previously,¹ quinoxaline reacts readily with nucleophiles. Two molecular proportions of Grignard reagent can be added. Thus, 2,3-bis[3-(dimethylamino)propyl]-1,2,3,4-tetrahydroquinoxaline (**65**) results from quinoxaline and 3-(dimethylamino)propylmagnesium chloride. Compound **65** can be dehydrogenated to the corresponding quinoxaline. 2-Quinoxalinone (**60**) adds 1 mole of methylmagnesium iodide or phenylmagnesium bromide to yield the corresponding 3-substituted tetrahydroquinoxalinones **66**.⁸⁴

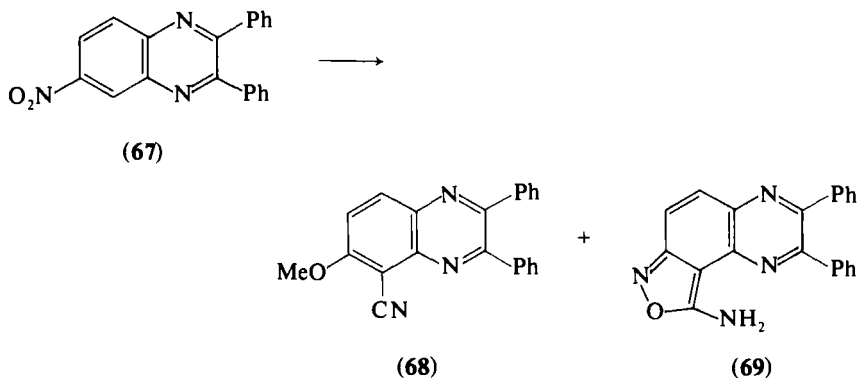


R = Me or Ph

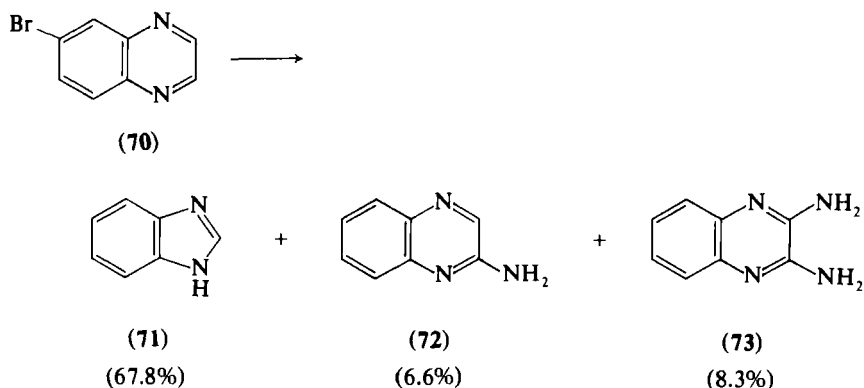
6-Substituted quinoxalines undergo unusual reactions with nucleophiles. Thus, 2,3-diphenyl-6-nitroquinoxaline (**67**) with potassium cyanide undergoes substitution in the 5-position, with simultaneous nucleophilic displacement of the 6-nitro group by the methanol solvent to give compound **68** (52%); 5-aminoisoxazolo[4,3-*f*]quinoxaline (**69**) is also obtained (35%). The structure of the product **68** was proved by an unambiguous synthesis.⁸⁵

⁸⁴ A. Marxer, U. Salzmann, and F. Hofer, *Helv. Chim. Acta* **54**, 2507 (1971).

⁸⁵ H. Takashi and H. Otomasu, *Chem. Pharm. Bull.* **18**, 22 (1970).



6-Bromoquinoxaline (70) with KNH_2 in NH_3 undergoes ring contraction, to give benzimidazole (71) as the predominant product, together with some 2-amino- (72), and 2,3-diamino- (73) quinoxaline, but only traces of the expected 6-amino derivative.⁸⁶ More recently, similar treatment of 6-chloroquinoxaline yielded 2-amino-7-chloroquinoxaline and 2,3-diamino-6-chloroquinoxaline.⁸⁷ 6-Bromo-2,3-dimethylquinoxaline under these conditions gave 5- and 6-amino derivatives, presumably via 5,6-didehydro-2,3-dimethylquinoxaline.⁸⁸ Benzimidazole (71) is also the predominant product from 2-bromoquinoxaline and KNH_2 in NH_3 .⁸⁹ 6-Nitroquinoxalines are aminated in the 5-position by hydroxylamine.⁹⁰



⁸⁶ W. Czuba and H. Poradowska, *Rocz. Chem.* **48**, 1233 (1974).

⁸⁷ H. Poradowska and W. Czuba, *Univ. Adama Mickiewicza Poznaniu, Wydz. Mat. Fiz. Chem. (Pr) Ser. Chem.* **18**, 299 (1975) [*CA* **84**, 120749 (1976)].

⁸⁸ W. Czuba and H. Poradowska, *Rec. Trav. Chim. Pays-Bas* **93**, 162 (1974).

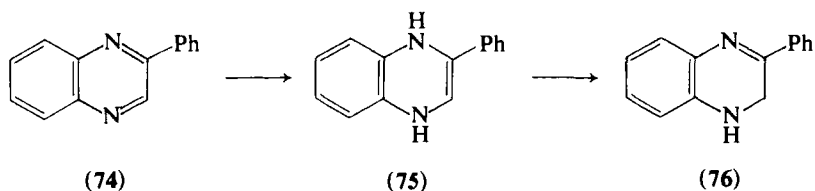
⁸⁹ P. J. Lont and H. C. van der Plas, *Rec. Trav. Chim. Pays-Bas* **91**, 85 (1972).

⁹⁰ R. Nasielski-Hinkins and M. Benedek-Vamos, *J. Chem. Soc., Perkin Trans. 1*, 1229 (1975).

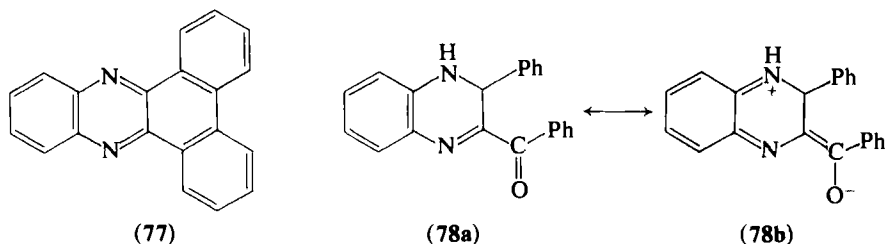
B. REDUCTION

1. Dihydroquinoxalines

Reduction of quinoxaline with sodium in tetrahydrofuran (THF) at 20° yields 1,4-dihydroquinoxaline (26%).⁹¹ A 1,4-dihydroquinoxaline (**75**) is also the first product of reduction of 2-phenylquinoxaline (**74**), but **75** readily rearranges to the thermodynamically more stable 1,2-dihydro isomer (**76**).⁹²



Attempted reduction of 2,3-diphenylquinoxaline by lithium results in cyclodehydrogenation to dibenzo[*a,c*]phenazine (**77**).⁹³ 2-Benzoyl-3-phenylquinoxaline is reduced by sodium amalgam to the red 2-benzoyl-3,4-dihydro-3-phenylquinoxaline (**78a** ↔ **78b**).⁹⁴



Acetic anhydride cyclization of the 2-hydroxyphenyl-3,4-dihydroquinoxaline **79** yields the benzopyranoquinoxaline derivative **80**.⁹⁵ Some 1,2-dihydro-2-arylquinoxalines have herbicidal activity.⁹⁶

⁹¹ J. Hamer and R. E. Holliday, *J. Org. Chem.* **28**, 2488 (1963).

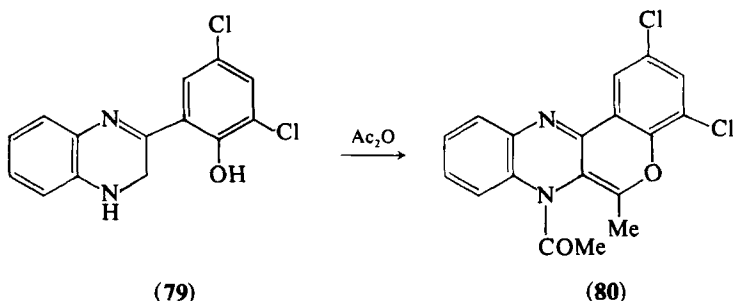
⁹² M. Schellenberg, *Helv. Chim. Acta* **53**, 1151 (1970).

⁹³ J. G. Smith and E. M. Levi, *J. Organomet. Chem.* **36**, 215 (1972).

⁹⁴ C. Brandt, G.v. Foerster, and F. Kröhnke, *Justus Liebigs Ann. Chem.* **688**, 189 (1965).

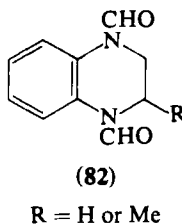
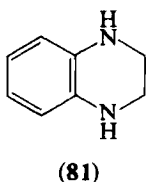
⁹⁵ J. Curtze and K. Thomas, *Justus Liebigs Ann. Chem.*, 328 (1974).

⁹⁶ M. T. Clark, Shell Research Ltd. (Sittingbourne, Kent, England), personal communication.



2. Tetrahydroquinoxalines

Reduction of quinoxaline with lithium aluminum hydride in ether yields 43% of 1,2,3,4-tetrahydroquinoxaline (**81**),⁹¹ also obtained in 20% yield by reduction with sodium in refluxing alcohol. Both sodium borohydride in acetic acid,⁹⁷ and hydrogen and platinum,¹⁸² have been used to reduce 6-substituted quinoxalines to the 1,2,3,4-tetrahydro compounds. Quinoxaline and its 2-methyl derivative undergo reductive formylation when treated with formic acid in formamide; 1,4-diformyl-1,2,3,4-tetrahydroquinoxalines (**82**) are the main products isolated.⁹⁸ *Cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxalines have been synthesized, and their conformation studied by NMR. Both isomers are conformationally mobile, down to -87° . In the *trans* compound, NMR indicates that H-2 and H-3 are predominantly in the *axial* orientation, and in the spectrum of the *cis* compound there is an average signal representing rapidly interconverting equivalent axial and equatorial hydrogens.⁹⁹ (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline has been unequivocally synthesized from L- α -alanine.¹⁰⁰



5-Amino-1,2,3,4-tetrahydroquinoxalin-2-ones (**83**) [obtained by reduction of *N*-(2,6-dinitrophenyl)- α -amino acids] undergo ring closure

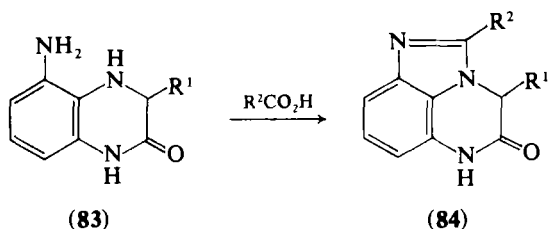
⁹⁷ K. V. Rao and D. Jackman, *J. Heterocycl. Chem.* **10**, 213 (1973).

⁹⁸ I. Baxter and D. W. Cameron, *J. Chem. Soc. C*, 2471 (1968).

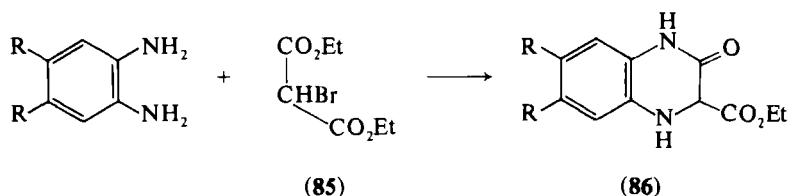
⁹⁹ R. A. Archer and H. A. Mosher, *J. Org. Chem.* **32**, 1378 (1967).

¹⁰⁰ G. H. Fisher, P. J. Whitman, and H. P. Schultz, *J. Org. Chem.* **35**, 2240 (1970).

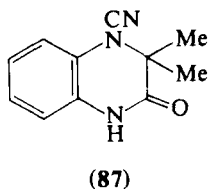
with carboxylic acids, and 5,6-dihydro-4*H*-imidazo[1,5,4-*de*]quinoxalin-2-ones (**84**) are formed.¹⁰¹



2-Ethoxycarbonyl-1,2,3,4-tetrahydroquinoxalin-2-ones (**86**) are obtained either by sodium dithionite reduction of the corresponding quinoxalinone esters or by direct synthesis from *o*-phenylenediamines and bromomalonic ester (**85**).¹⁰²



3,3-Dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one with cyanogen bromide gives the *N*-cyanoquinoxaline (**87**).¹⁰³



Recently, the chiralities of the bridge-carbon atoms of (+) and (–)-*trans*-decahydroquinoxalines have been established and correlated with those of (+)-*trans*-cyclohexane-1(*S*),2(*S*)-dicarboxylic acid, and (+)-*trans*-cyclohexane-1(*S*),2(*S*)-diamine.¹⁰⁴

2-Substituted-1,2,3,4-tetrahydroquinoxalines undergo monotosylation at N-1, but benzylation occurs at N-4. The tosyl derivatives have

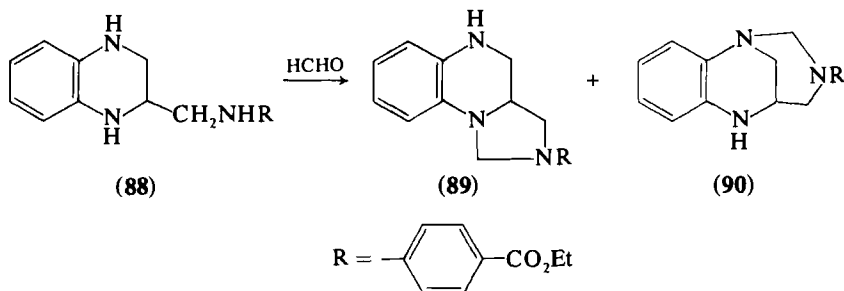
¹⁰¹ H. Otomasu, S. Ohmiya, H. Takahashi, K. Yoshida, and S. Sato, *Chem. Pharm. Bull.* **21**, 353 (1973).

¹⁰² Y. Ahmad, M. S. Habib, M. Iqbal, and M. I. Qureshi, *J. Chem. Soc.* 4053, 4056 (1964).

¹⁰³ C. W. Bird, *Tetrahedron* **21**, 2179 (1965).

¹⁰⁴ D. Gracian and H. P. Schultz, *J. Org. Chem.* **36**, 3989 (1972).

been used to establish the C-2 chiralities of various 2-substituted 1,2,3,4-tetrahydroquinoxalines. (*S*)-1-*p*-Tosyl-2-methyl-1,2,3,4-tetrahydroquinoxaline is identical with the configurational standard prepared directly from L- α -alanine.¹⁰⁵ Tetrahydroquinoxalines, such as the ester **88**, are of interest as structural analogs of tetrahydrofolic acid, a compound with a vital role in one-carbon metabolism. The reactions of compound **88** with formaldehyde lead to both imidazoline (**89**) and hexahydropyrimidine (**90**) formation. The pyrimidine moiety in tetrahydrofolic acid may deactivate N-8 (corresponding to N-4 in the quinoxaline) and so prevent ring closure with formaldehyde to a hexahydropyrimidine.^{106, 107}



C. N-OXIDE FORMATION

Various peracids have been used for the N-oxidation of quinoxalines, but the most convenient reagent for many 2-substituted and 2,3-disubstituted quinoxalines is 30% aqueous hydrogen peroxide in acetic acid. With this reagent, oxidation has been carried out at temperatures ranging from 20° to 90°.^{108–112} For example, 2-methyl-3-phenylquinoxaline (**91**) when treated with peroxide and acetic acid at 56° for 14 hours yields a mixture of the 1-oxide (**92**) and the 1,4-dioxide (**93**).¹¹²

¹⁰⁵ G. H. Fisher and H. P. Schultz, *J. Org. Chem.* **39**, 635 (1974).

¹⁰⁶ G. P. Tuszynski, M. Frederick, and R. G. Kallen, *J. Am. Chem. Soc.* **97**, 7359 (1975).

¹⁰⁷ S. J. Benkovic, T. H. Barrows, and P. R. Farina, *J. Am. Chem. Soc.* **95**, 8414 (1973).

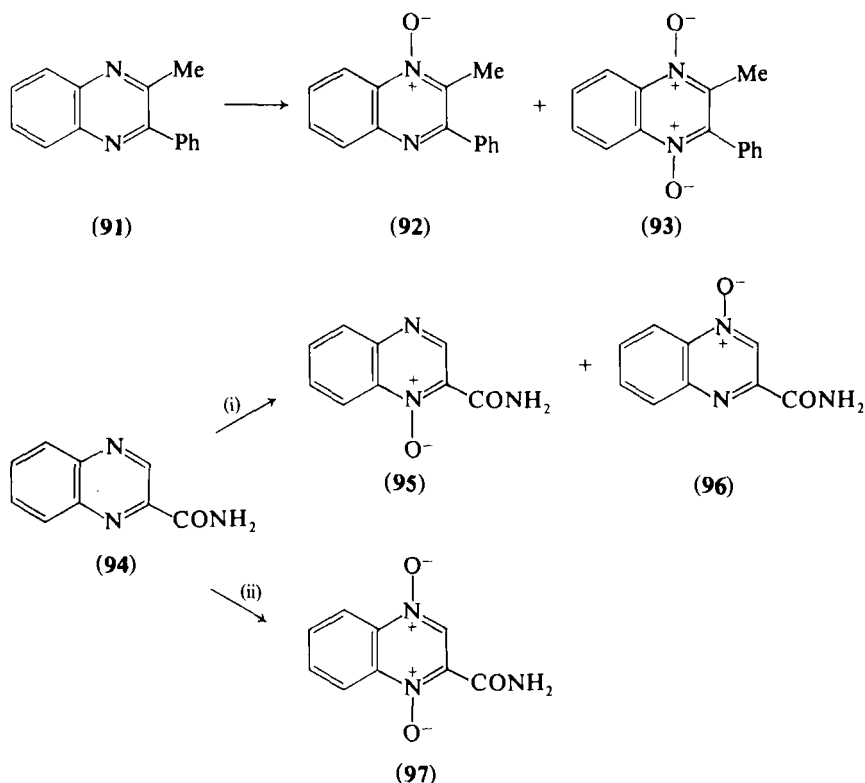
¹⁰⁸ A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides." Academic Press, New York, 1971.

¹⁰⁹ E. Hayashi and C. Iijima, *Yakugaku Zasshi* **84**, 156 (1964) [*CA* **61**, 3108 (1964)].

¹¹⁰ A. S. Elina, E. N. Padeiskaya, O. Yu. Magidson, G. N. Pershin, K. A. Belozerova, and V. T. Fatneva, U.S.S.R Patent 320,495 (1971) [*CA* **76**, 99706 (1972)].

¹¹¹ A. S. Elina and L. G. Tsyrlnikova, *Zh. Obshch. Khim.* **33**, 1544 (1963) [*CA* **59**, 12807 (1963)].

¹¹² W. E. Hahn, Z. Kedzierska, and B. Muszkiet, *Lodz. Tow. Nauk. Pr. Wyd. 3 Acta Chim.* **15**, 77 (1970) [*CA* **75**, 98536 (1971)].



Reagents: $\text{MeCO}_3\text{H}-\text{NaOAc}$ (i) $20^\circ\text{--}25^\circ/48$ hours (ii) $45^\circ\text{--}48^\circ/22$ hours

Peracetic acid oxidation of 2-carbamoylquinoxaline (94) at $20^\circ\text{--}25^\circ$ gives the monoxides 95 and 96, and at higher temperatures the 1,4-dioxide (97) is isolated in 50% yield, together with a small amount of the 1,4-dioxide of 2-amino-3-quinoxalinone.¹¹¹ However, Hayashi and co-workers report the isolation of *only* 96 from 94 using monoperphthalic acid in ether $<10^\circ$.¹⁰⁹ In their attempt to correlate the nature of 2-substitution with the formation of 1- versus 4-oxides, they examined the behavior of some 2-alkyl substituted quinoxalines:^{113,114} 2-ethylquinoxaline gives the 1- and 4-oxides and the 1,4-dioxide, 2-isopropylquinoxaline yields the 4-oxide and the 1,4-dioxide; however, 2-*t*-butylquinoxaline only furnishes the 4-oxide because of steric hindrance.¹¹⁴ The N-oxidation of 2-phenyl- and 2-alkyl-3-phenyl-quinoxalines with monoperphthalic acid furnishes the products shown in Table I.¹¹⁴

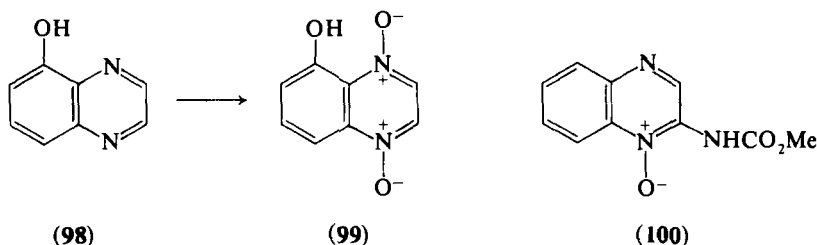
¹¹³ E. Hayashi, C. Iijima, and K. Yamamoto, *Yakugaku Zasshi* **86**, 1109 (1966) [*CA* **67**, 3066 (1967)].

¹¹⁴ E. Hayashi and Y. Miura, *Yakugaku Zasshi* **87**, 643 (1967) [*CA* **67**, 90774 (1967)].

TABLE I
N-OXIDATION OF QUINOXALINES WITH MONOPERPHTHALIC ACID

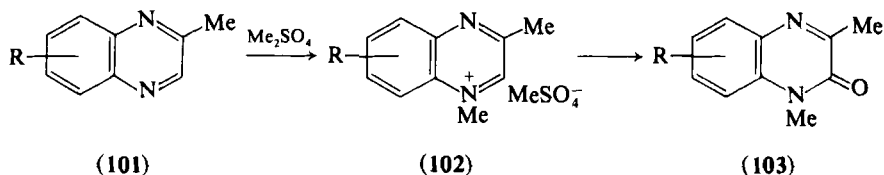
	1-Oxide	4-Oxide	1,4-Dioxide
2-Phenylquinoxaline	90%	Small	Small
2-Methyl-3-phenylquinoxaline	65%	0	Small
2-Ethyl-3-phenylquinoxaline	19%	0	48%
2-Isopropyl-3-phenylquinoxaline	Trace	76%	Trace

5-Hydroxyquinoxaline (**98**) is converted into the 1,4-dioxide (**99**), and 5-acetamido-7-methylquinoxaline similarly forms the 1,4-dioxide with *m*-chloroperbenzoic acid in benzene.^{195a, b} 2-Aminoquinoxaline is best oxidized with permaleic acid in ethanol in the presence of sodium bicarbonate. Exclusive 1-oxidation occurs, and the product is conveniently isolated as the carbamic acid ester (**100**) (85%).¹¹⁵



D. QUINOXALINE QUATERNARY SALTS

During the last few years, numerous quaternary salts of quinoxalines have been prepared, and their reactions studied. 2-Methylquinoxaline and some of its 6,7-substituted derivatives (**101**) form 4-methylquinoxalinium methosulfates and perchlorates (**102**).¹¹⁶ On hydrolysis of these salts, the quinoxalinones (**103**) are formed. Similarly 2,3-dimethyl-

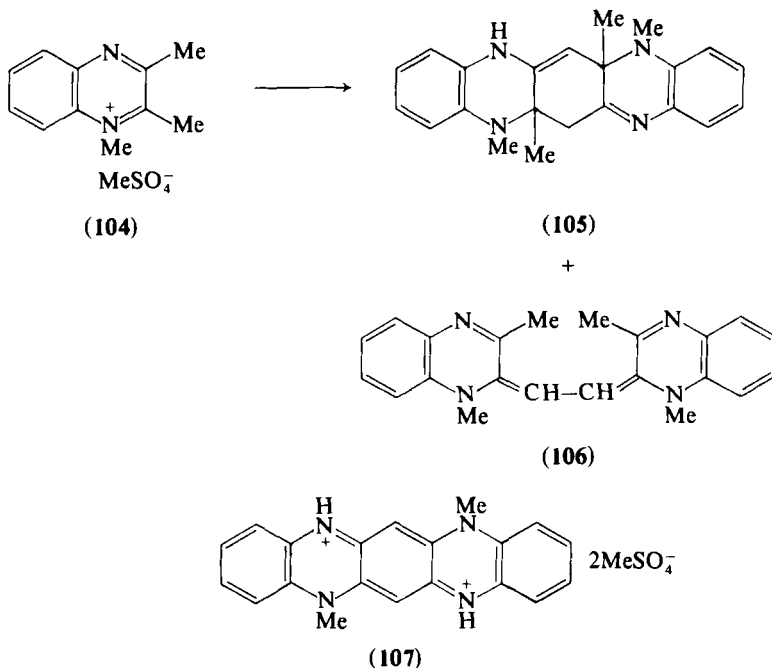


R = 6- or 7-Me, 6- or 7-Cl, 6-NO₂, 6-NH₂, 6-NHAc

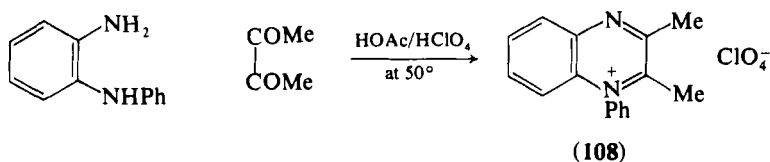
¹¹⁵ R. A. Burrell, J. M. Cox, and E. G. Savins, *J. Chem. Soc., Perkin Trans. 1*, 2707 (1973).

¹¹⁶ H. Wahl, M. T. Le Bris, and D. Berkovitch, *Bull. Soc. Chim. Fr.*, 1285 (1973).

quinoxaline is quaternized with dimethyl sulfate, and 1,2,3-trimethylquinoxalinium methosulfate (**104**) is isolated.¹¹⁷ On standing in sodium phosphate buffer at pH 7.5–8.0, **104** dimerizes to two colored compounds, a major yellow product, **105** and **106**¹¹⁸; the structures were proved spectroscopically. The oxidation product of 2-methylquinoxalinium methosulfate (**102**, R=H) has recently been identified as the salt of the quinoxalinophenazine **107**.¹¹⁹



1-Alkyl- and 1-aryl-2,3-dimethylquinoxalinium perchlorates are synthesized by the condensation of biacetyl with suitably substituted *o*-phenylenediamines in strong acid. Thus, 1-phenyl-2,3-dimethylquinoxalinium perchlorate (**108**) was obtained (93% yield).¹²⁰



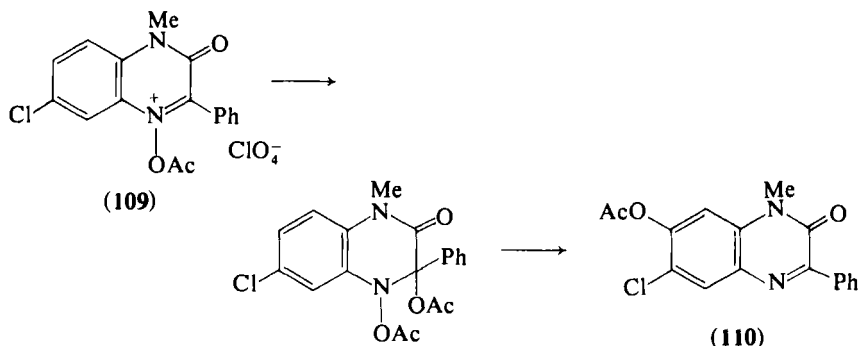
¹¹⁷ M. T. Le Bris, *Bull. Soc. Chim. Fr.*, 563 (1970).

¹¹⁸ M. T. Le Bris, *Bull. Soc. Chim. Fr.*, 2270 (1970).

¹¹⁹ H. Wahl, M. T. Le Bris, and D. Berkovitch, *Bull. Soc. Chim. Fr.*, 1289 (1973).

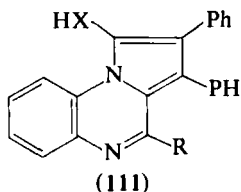
¹²⁰ D. Schelz and M. Priester, *Helv. Chim. Acta* **58**, 317 (1975).

Tennant and Livingstone have reported the preparation, and some substitution reactions, of 1-acetoxy-3,4-dihydro-3-oxo-2-phenylquinoxalinium perchlorates (e.g., **109**). With sodium acetate, **109** gives the 6-acetoxyquinoxalinone **110** via an intermediate tetrahydroquinoxaline.¹²¹



E. CYCLOADDITION REACTIONS

Quinoxaline and 2-methylquinoxaline form 1:1 adducts (**111**) with diphenylcyclopropenone,¹²² and an analogous pyrrolo[1,2-*a*]quinoxaline has been isolated from the reaction of quinoxaline with diphenylcyclopropenethione.¹²³



R = H or Me; X = O or S

IV. Properties and Reactions of Some Substituted Quinoxalines

A. REACTIVITY OF α -METHYL GROUPS

α -Methylquinoxalines exhibit the typical reactivity of active methyl compounds. Condensation with aldehydes¹²⁴⁻¹²⁶ proceeds readily;

¹²¹ D. B. Livingstone and G. Tennant, *Chem. Ind. (London)*, 848 (1973).

¹²² J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 1165 (1971).

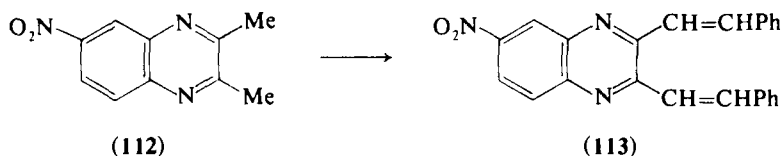
¹²³ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 3119 (1971).

¹²⁴ (a) C. S. Mahajanshetti and S. Siddappa, *Indian J. Chem.* **1**, 541 (1963); (b) A. Jonsson, P. Stene, and N. Willman, *Acta Pharm. Suec.* **5**, 237 (1968) [*CA* **69**, 86957 (1968)].

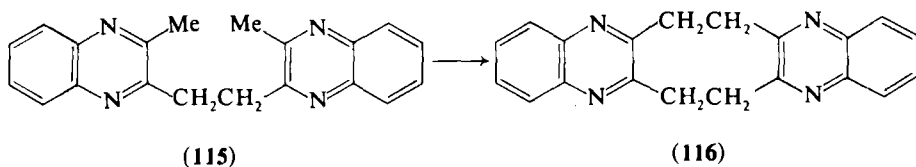
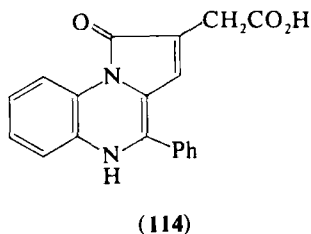
¹²⁵ (a) J. Klicnar, F. Kosek, and S. Panusova, *Collect. Czech. Chem. Commun.* **29**, 206 (1964); (b) J. Klicnar, M. Vavra, P. Vetesnik, and S. Panusova, *Sb. Ved. Pr., Vys. Sk. Chemickotechnol., Pardubice* **18**, 15 (1968) [*CA* **72**, 66896 (1970)].

¹²⁶ J. Karalek, *Collect. Czech. Chem. Commun.* **34**, 1819 (1969).

thus, 2,3-dimethyl-6-nitroquinoxaline (**112**) with benzaldehyde in acetic anhydride rapidly yields 2,3-distyryl-6-nitroquinoxaline (**113**).¹²⁵ The reaction of benzaldehyde with 2,3-dimethylquinoxaline is kinetically first order with respect to both aldehyde and dimethylquinoxaline.¹²⁶ Oxidation with permanganate of **112** furnishes 6-nitroquinoxaline 2,3-dicarboxylic acid.¹²⁵



2-Methyl-3-phenylquinoxaline reacts with maleic anhydride to give 2-carboxymethyl-4-phenylpyrrolo[1,2-*a*]quinoxalin-1(5*H*)-one (**114**). Decarboxylation of the adduct gave the corresponding 2-methyl derivative, the structure of which was proved by an independent synthesis.¹²⁷ 2,3-Dimethylquinoxaline on treatment with phenyllithium and Cu_2Cl_2 undergoes dehydrodimerization to yield compound **115**. This has been further converted into the pentacyclic compound (**116**).¹²⁸

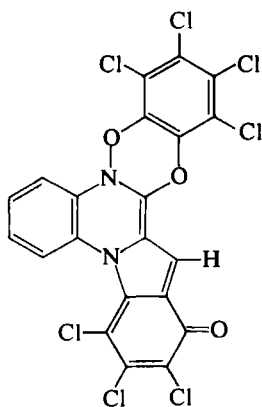


2-Methylquinoxaline is reported to give a polycyclic derivative (**117**) related to quinoxaline orange with 2-equivalents of tetrachloro-1,2-benzoquinone; 2-(2-quinoxalino)-4,5,6,7-tetrachlorobenzo-1,3-dioxole (**118**) is also formed. 2,3-Dimethyl- and 2,3-dibenzyl-quinoxalines give addition products similar to **118**.¹²⁹

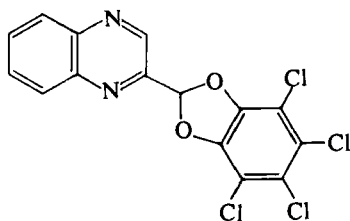
¹²⁷ E. C. Taylor and G. W. H. Cheeseman, *J. Am. Chem. Soc.* **86**, 1830 (1964).

¹²⁸ T. Kauffmann, D. Kuhlmann, W. Sahm, and H. Schrecken, *Angew. Chem., Int. Ed. Engl.* **7**, 541 (1968).

¹²⁹ J. W. Lown, R. Westwood, and A. S. K. Aidoo, *Can. J. Chem.* **48**, 327 (1970).

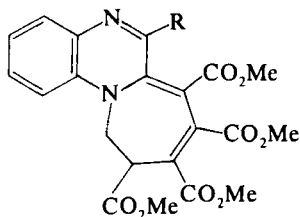


(117)



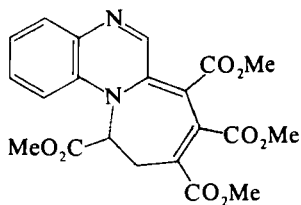
(118)

2-Methylquinoxaline reacts with dimethyl acetylenedicarboxylate to give a mixture of the azepino[1,2-*a*]quinoxalines **119** and **120**, product formation involving migration of an ester group. 2,3-Dimethylquinoxaline yields the azepinoquinoxaline **121** and a second product, **122**, the structure of which was not proved unambiguously and which may

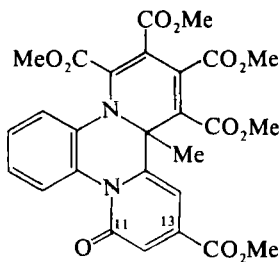


(119) R = H

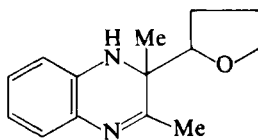
(121) R = Me



(120)



(122)



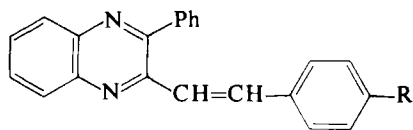
(123)

have the carbonyl and ester groups at positions 11 and 13 interchanged.¹³⁰

2,3-Dimethylquinoxaline reacts with ethers under photolytic conditions by 1,2-addition: in tetrahydrofuran, 2-(2-tetrahydrofuryl)-2,3-dimethyl-1,2-dihydroquinoxaline (**123**) is isolated.¹³¹

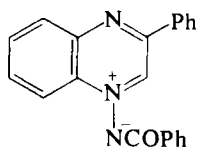
B. α -PHENYLQUINOXALINES

2-Methyl-3-phenylquinoxaline reacts with aryl aldehydes to form 2-styryl derivatives (**124**), but forcing conditions (reflux in oil bath for 12–15 hours) are necessary to overcome the steric effect of the 3-phenyl group.¹²⁴ Direct N-amination of 2-phenylquinoxaline has been reported with *O*-mesitylsulfonylhydroxylamine. The reactive nitrogen is N-4, the least sterically hindered, and the product was characterized by conversion into the *N*-benzoylimine (**125**).¹³²



(124)

R = Me, OMe or Cl



(125)

The product of reaction between 2,3-diphenylquinoxaline and potassium amide has now been assigned as 2-phenylbenzimidazole,¹³³ rather than 2,2-diphenyl-3-amino-1,2-dihydroquinoxaline, as suggested earlier.

C. α -(SUBSTITUTED METHYL)QUINOXALINES

2,3-Bis(bromomethyl)quinoxaline (**126**) is better prepared by the condensation of *o*-phenylenediamine and 1,4-dibromobutane-2,3-dione than by side-chain bromination of 2,3-dimethylquinoxaline. It reacts with secondary amines, forming quinoxalino[2,3-*c*]pyrrolidine salts, e.g. (**127**).¹³⁴ Reaction with thiols yields 2,3-bis(thiomethyl)quinoxalines,¹³⁵

¹³⁰ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 378 (1968).

¹³¹ T. T. Chen, W. Doerscheln, H. Goeth, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **51**, 632 (1968).

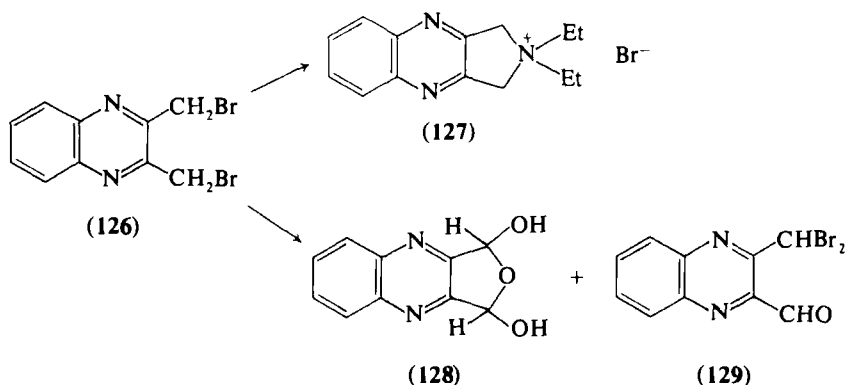
¹³² Y. Tamura, Y. Miki, J. Minamikawa, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 675 (1974).

¹³³ E. C. Taylor and A. McKillop, *J. Org. Chem.* **30**, 2858 (1965).

¹³⁴ (a) W. E. Hahn and J. Z. Lesiak, *Soc. Sci. Lodz., Acta Chim.* **17**, 201 (1972) [*CA* **78**, 58357 (1973)]; (b) W. E. Hahn and J. Z. Lesiak, Polish Patent 71,049 (1974) [*CA* **83**, 28279 (1975)].

¹³⁵ C. Egli, Ger. Offen. 2,132,175 (1972) [*CA* **76**, 113251 (1972)].

useful as antiviral agents. Dimethyl sulfoxide oxidation of **126** is reported to give varying amounts of 3-methyl-2-bromomethylquinoxaline and 3-dibromomethylquinoxaline-2-carboxaldehyde (**129**), in addition to 2,3-bis(dibromomethyl)quinoxaline and 2,3-quinoxalinedicarboxyaldehyde, isolated as its cyclic hemihydrate (**128**). At 90° for 45 minutes, 60% of compound **128** and 30% of compound **129** are obtained.¹³⁶ 2-(Nitromethyl)quinoxaline, prepared by ring closure of *o*-phenylenediamine with sodium 2-nitro-3-oxosuccinaldehyde ($\text{HCO} \cdot \text{COCH}(\text{NO}_2)\text{CO}_2\text{Na}$), when treated with an excess of diazomethane gives quinoxaline 2-aldoxime, dehydration of which (Ac_2O) yields 2-cyanoquinoxaline.¹³⁷



D. TAUTOMERISM OF 3-SUBSTITUTED 2-QUINOXALINONES

3-Substituted 2-quinoxalinones carrying an acyl-methyl function in the 3-position exhibit side chain–ring tautomerism,^{35, 138–141} with the two tautomeric forms, **130** and **131**, contributing. The position of the equilibrium depends on solvent and temperature¹³⁹ and has been studied, where, e.g., $\text{R} = \text{Ph}$ ¹³³ or CO_2Et ,^{138, 139} by spectroscopic techniques (IR, NMR, and UV). Thus for 3-phenacyl-2(1*H*)-quinoxalinone, the enamine form (**132**) is an important contributor.¹⁴⁰ Intramolecular hydrogen bonding is thought to contribute to the stability of the enamine tautomer. Similarly, 3-ethoxycarbonylmethyl-2(1*H*)-quinoxalinone is thought to exist predominantly in the hydrogen-

¹³⁶ E. J. Moriconi and A. J. Fritsch, *J. Org. Chem.* **30**, 1542 (1965).

¹³⁷ P. E. Fanta and C. S. Wang, *J. Heterocycl. Chem.* **3**, 525 (1966). (b) **3**, 367 (1966).

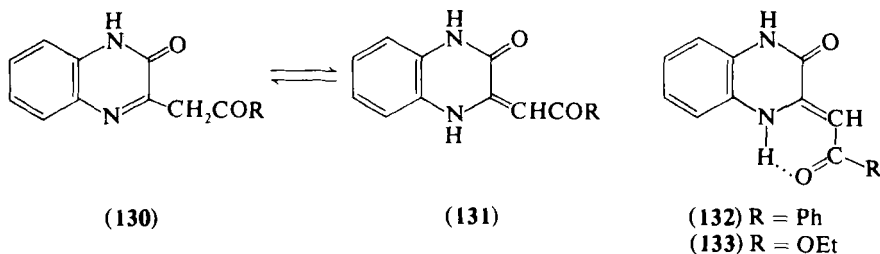
¹³⁸ (a) R. Mondelli and L. Merlini, *Nucl. Magn. Reson. Chem., Proc. Symp.*, 243 (1964) [*CA* **66**, 2078 (1967)]; (b) *Tetrahedron* **22**, 3253 (1966).

¹³⁹ H. Sterk and T. Kappe, *Monatsh. Chem.* **100**, 1274 (1969).

¹⁴⁰ Y. Iwanami, T. Seki, and T. Inagaki, *Bull. Chem. Soc. Jpn.* **44**, 1316 (1971).

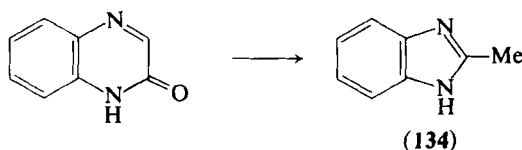
¹⁴¹ D. D. Chapman, *J. Chem. Soc. C*, 806 (1966).

bonded enamine form (133) at low temperatures, but at higher temperatures the alternative tautomeric form becomes significant.¹³⁹



E. REACTIONS OF QUINOXALIN-2-ONES AND QUINOXALINE-2,3-DIONES

Quinoxaline-2,3-dione is converted into 2,3-dichloroquinoxaline by phosphoryl chloride¹⁴² or phosphorus pentachloride.¹⁴³ 2,3-Dibromoquinoxaline is similarly obtained using phosphoryl bromide in dimethylaniline.¹⁴⁴ Quinoxalin-2-one undergoes ring contraction to 2-methylbenzimidazole (134) with hydrazine¹⁴⁵; however, quinoxaline-2,3-dione gives 3-hydrazino-2-quinoxalinone.¹⁴⁵ Quinoxalin-2-one yields a 3-*p*-dimethylaminophenyl derivative with *N,N*-dimethylaniline (in AcOH, with NH_4NO_3), and a 3-(indol-3-yl) derivative with indole.¹⁴⁶



Direct amination of quinoxalinones with hydroxylamine-*O*-sulfonic acid produces the 1-amino derivatives (135) in 70–80% yield, and subsequent oxidation with lead tetraacetate gives the 1,2,4-benzotriazines (138). Benzotriazine formation probably involves the formation of an intermediate nitrene (136), ring expansion to a benzo-triazepinone (137) and subsequent loss of carbon monoxide. The nitrene (136; R = Ph) was “trapped” as the sulfoximide 139 when the oxidation was carried out in the presence of dimethyl sulfoxide.¹⁴⁷

¹⁴² K. Winterfeld and M. Wildersohn, *Arch. Pharm.* **303**, 1002 (1970).

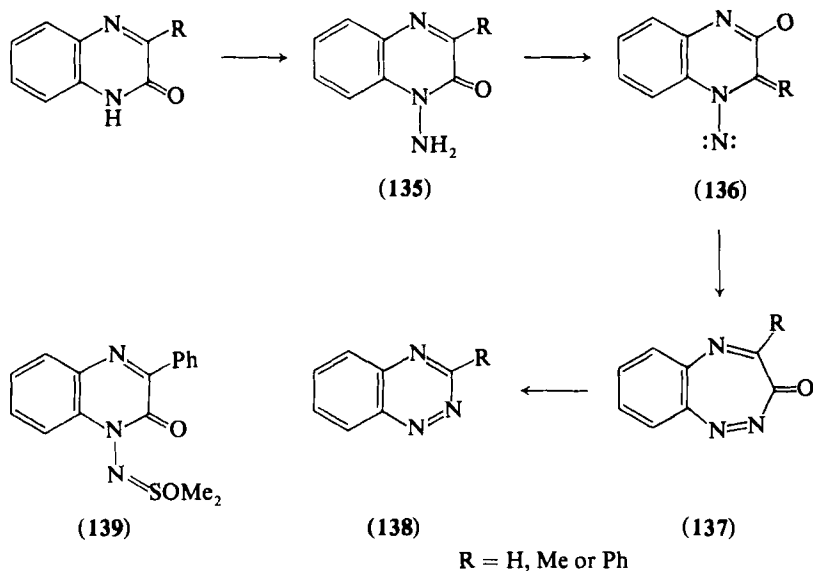
¹⁴³ K. Zauer, M. T. Gzygoryan, and E. A. Markaryan, *Khim. Geterotsikl. Soedin.* **9**, 43 (1972) [*CA* **79**, 126452 (1973)].

¹⁴⁴ C. Sosnowski and L. Wojciechowski, Polish Patent 61,711 (1971) [*CA* **74**, 125728 (1971)].

¹⁴⁵ G. W. H. Cheeseman and M. Rafiq, *J. Chem. Soc. C*, 452 (1971).

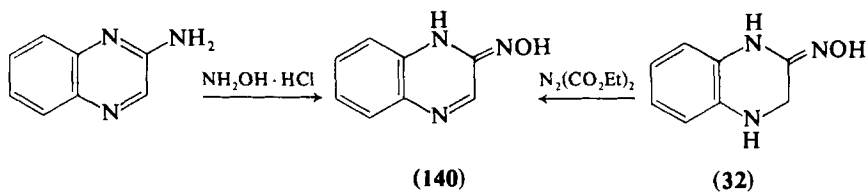
¹⁴⁶ O. N. Chupakin, E. O. Sidorov, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 993 (1974); 1433 (1975) [*CA* **81**, 120578 (1974); **84**, 43979 (1976)].

¹⁴⁷ C. W. Rees, B. Adger, A. A. Sale, and R. C. Storr, *Chem. Commun.*, 695 (1971).



F. NUCLEOPHILIC SUBSTITUTION REACTIONS OF 2- AND 2,3-DISUBSTITUTED QUINOXALINES

2-Aminoquinoxaline reacts with hydroxylamine hydrochloride to give 2-(hydroxyimino)-1,2-dihydroquinoxaline (**140**), also formed by dehydrogenation of 2-(hydroxyimino)tetrahydroquinoxaline (**32**) with diethyl diazodicarboxylate.¹⁴⁸

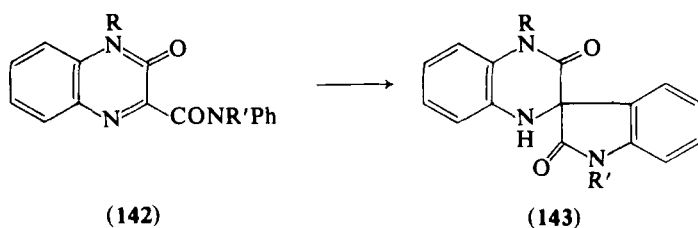
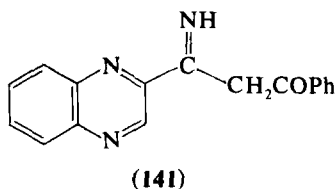


2-Cyanoquinoxaline reacts with carbanions either at the ring, with displacement of cyanide ion, or at the carbon of the cyano group. Thus acetophenone yields both 2-(2-quinoxaliny)acetophenone and 3-(2-quinoxaliny)-3-iminopropiophenone (**141**).¹⁴⁹ Quinoxalinecarboxanilides **142** undergo intramolecular cyclization to the spiroindoles **143**,

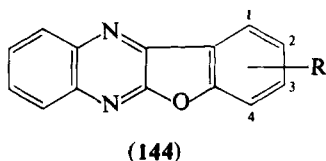
¹⁴⁸ K. Harsanyi, C. Gonczi, and D. Korbónits, *Justus Liebigs Ann. Chem.*, 190 (1973).

¹⁴⁹ E. Hayashi and S. Suzuki, *Yakugaku Zasshi* **93**, 881 (1973).

when heated in ethanolic hydrochloric acid. Nucleophilic attack of the activated aromatic ring at C-3 of the quinoxaline is facilitated by protonation of the adjacent ring nitrogen.¹⁰²



2-Chloroquinoxaline undergoes facile nucleophilic displacement reactions with amines¹⁵⁰ and aryloxides¹⁵¹ to give the corresponding 2-substituted quinoxalines. With diamines, besides the 2-amino derivatives, bis(quinoxaliny)alkylenediamines are produced.¹⁵⁰ When 2-chloroquinoxaline is treated with a sodium aryloxide in an excess of the corresponding phenol, a mixture of the expected 2-aryloxyquinoxaline and the corresponding benzofuro[2,3-*b*]quinoxaline (144) is obtained.¹⁵¹ 2-Aryloxyquinoxalines are readily cyclized with polyphosphoric acid to benzofuro[2,3-*b*]quinoxalines.¹⁵¹ 2-Arylfuro[2,3-*b*]quinoxalines (146) result from cyclization of 2-phenacyl-3-quinoxalinones (145).¹⁵²

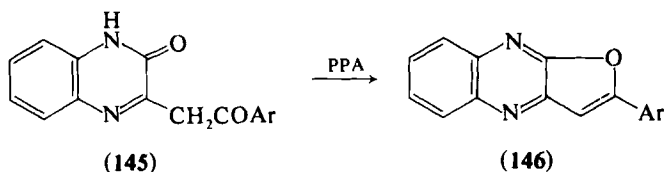


R = 3-Me; 3-OMe; 1,3-, 1,4-, and 3,4-diMe

¹⁵⁰ Z. Kolodynska and S. Biniecki, *Acta Pol. Pharm.* **20**, 285 (1963) [*CA* **62**, 559 (1965)].

¹⁵¹ R. K. Anderson and G. W. H. Cheeseman, *J. Chem. Soc., Perkin Trans. 1*, 129 (1974).

¹⁵² (a) J. Klicnar, M. Hajek, J. Hoffmann, and M. Vecera, *Collect. Czech. Chem. Commun.* **36**, 262 (1971); (b) Yu. S. Andrieichikov, R. F. Saraeva, and A. L. Fridman, *Khim. Geterotsikl. Soedin.*, 259 (1973) [*CA* **78**, 136226 (1973)]; (c) U.S.S.R. Patent 405,883 (1973) [*CA* **81**, 37577 (1974)].



2-(5-Bromo-2-furyl)quinoxaline and 3-(5-nitro-2-furyl)-2-quinoxalinone, and numerous substituted derivatives, have been synthesized and found to be active antibacterials and antimicrobials.¹⁵³ 2-[2-(5-Nitro-2-furyl)vinyl]quinoxalines (**147**) have also been prepared, and some derivatives (6-nitro and 6-amino) were found to have high tuberculostatic activity.¹⁵⁴

Nucleophilic displacement of 2-chloro-3-phenylquinoxaline with methylamine at 100°–150° and with sodium phenoxide in excess of phenol at 100° gives the expected 2-methylamino- and 2-phenoxy-3-phenylquinoxalines.¹⁵⁵ 2-Chloroquinoxaline and its 3-phenyl derivative undergo ring closure with aminoacetaldehyde dimethylacetal to an imidazo[1,2-*a*]quinoxaline.¹⁵⁶ Nucleophilic substitution of 2-chloroquinoxaline with hydroxide ion in water is accelerated by cationic micelles and retarded by anionic micelles. These results were correlated with reactions of 1-chloro-2,4-dinitrobenzene, and the characteristics of their transition states were discussed.¹⁵⁷

2,3-Dichloroquinoxaline with anhydrous potassium fluoride at 200° yields 2,3-difluoroquinoxaline, which is readily hydrolyzed to quinoxaline-2,3-dione.¹⁵⁸ Treatment of 2,3-dichloroquinoxaline with phosphorus pentachloride at 300° yields hexachloroquinoxaline, which with potassium fluoride at 380° gives predominantly hexafluoroquinoxaline (**148**).¹⁵⁹

¹⁵³ (a) N. Saldabols, L. N. Alekseeva, B. Brizga, A. Zile, L. Kruzmetras, and K. Medne, *Khim.-Farm. Zh.* **2**, 14 (1968) [*CA* **70**, 37785 (1969)]; (b) N. Saldabols, A. Cimanis, J. Popelis, and S. Hillers, *Khim. Geterotsikl. Soedin.*, 404 (1973) [*CA* **78**, 147907 (1973)]; (c) N. Saldabols and A. Cimanis, U.S.S.R. Patent 410,015 (1974) [*CA* **80**, 120992 (1974)]; (d) A. F. Oleinik, G. A. Modnikova, K. Yu. Novitskii, T. A. Guskova, and G. N. Pershin, *Khim.-Farm. Zh.* **8**, 7 (1974) [*CA* **81**, 63554 (1974)].

¹⁵⁴ (a) T. Ohashi and K. Miura, Japanese Patent 68 04,356 [*CA* **69**, 96773 (1968)]; (b) M. Ikeda, T. Ohashi, Y. Igazashi, S. Matsuda, and K. Miura, Japanese Patent 69 04,785 [*CA* **71**, 3407 (1969)]; (c) N. Saldabols, L. N. Alekseeva, B. Brizga, K. Medne, L. Kruzmetra, and A. Zile, *Khim.-Farm. Zh.* **3**, 9 (1969) [*CA* **71**, 38908 (1969)].

¹⁵⁵ S. Tagami and D. Shiho, *Yakugaku Zasshi* **84**, 1085 (1964) [*CA* **62**, 5278 (1965)].

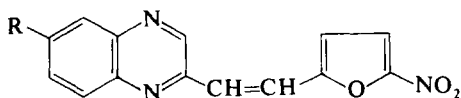
¹⁵⁶ R. F. Cookson and R. E. Rodway, *J. Chem. Soc., Perkin Trans. 1*, 1854 (1975).

¹⁵⁷ V. Flamini and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 421 (1975).

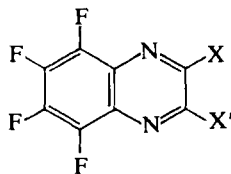
¹⁵⁸ J. Homer, *J. Heterocycl. Chem.* **3**, 244 (1966).

¹⁵⁹ (a) C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Ind. (London)*, 1402 (1968); (b) British Patent 1,274,445 (1972) [*CA* **77**, 48574 (1972)]; (c) *J. Fluorine Chem.* **1**, 59 (1971).

Displacement of α -fluorine atoms by nucleophiles is extremely fast: the rate of hydrolysis of 2-fluoropyrazine in 0.01 *N* NaOH at 26° is 240 times greater than that of 2-chloropyrazine.¹⁶⁰ Hexafluoroquinoxaline with 1 mole of sodium methoxide in methanol at -15° yields 2-methoxy-3,5,6,7,8-pentafluoroquinoxaline (**149**); with 2 moles, the 2,3-dimethoxy analog (**150**) is formed.¹⁵⁹



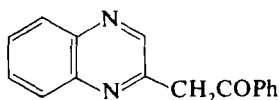
(147)



(148) X = X' = F

(149) X = F, X' = OMe

(150) X = X' = OMe



(151)

Reactions of 2-chloro- and 2,3-dichloroquinoxalines with carbanions give 2-quinoxaliny ketones and 3-chloro-2-quinoxaliny ketones, respectively e.g., 2-quinoxalinyacetophenone (**151**) from acetophenone anion.¹⁶¹ However, 2,3-dimethoxy- and 2,3-diethoxy-quinoxaline with methyl ethyl ketone and sodamide in anhydrous benzene give 2-amino derivatives rather than ketones.¹⁶²

2,3-Dichloroquinoxaline (**152**) is a starting material for the synthesis of condensed quinoxaline heterocyclic systems.^{163–165} Reaction of (**152**) with 2,3-dimercaptoquinoxaline (**153**) yields the [1,4]-dithiino[2,3-*b*:5,6-*b'*]diquinoxaline (**154**)¹⁶³ and with 4,5-diphenylimidazoline-2-thione (**155**) the imidazo[2',1'-2,3]thiazolo[4,5-*b*]quinoxaline (**156**) is obtained.¹⁶⁵

¹⁶⁰ H. Rutner and P. E. Spoerri, *J. Heterocycl. Chem.* **3**, 435 (1966).

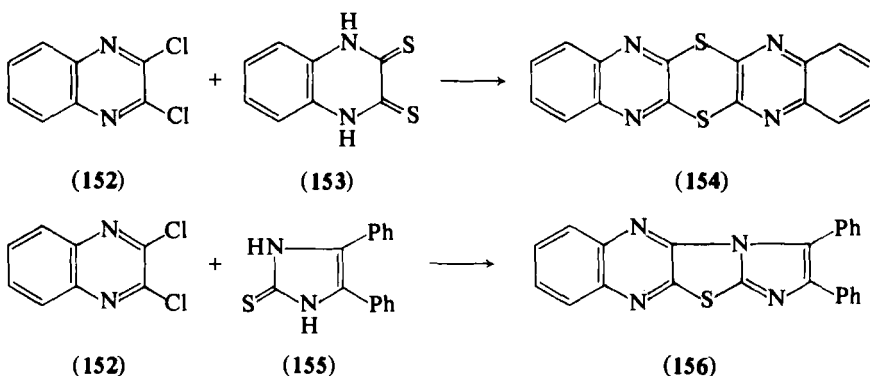
¹⁶¹ C. Iijima and E. Hayashi, *Yakugaku Zasshi* **92**, 729 (1972) [CA **77**, 88434 (1972)].

¹⁶² C. Iijima, T. Morikawa, and E. Hayashi, *Yakugaku Zasshi* **95**, 784 (1975) [CA **84**, 4901 (1976)].

¹⁶³ (a) L. Wojciechowski, *Rocz. Chem.* **43**, 1205 (1969); (b) **44**, 2461 (1970); (c) Polish Patent 65,740 (1972) [CA **77**, 140150 (1972)].

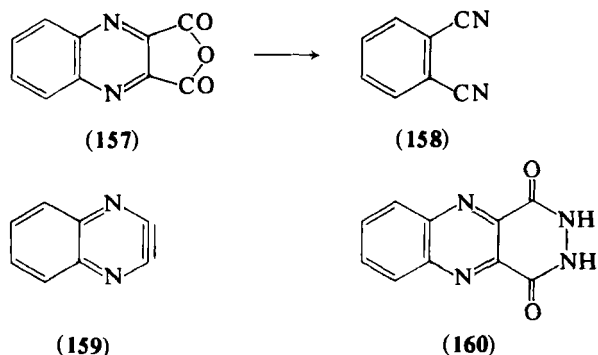
¹⁶⁴ S. Singh, H. Singh, and K. S. Narang, *J. Indian Chem. Soc.* **47**, 1150 (1970).

¹⁶⁵ (a) J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.* **11**, 747 (1973); (b) K. S. Dhaka, J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.* **12**, 287 (1974); (c) **12**, 966 (1974).



G. QUINOXALINE CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Quinoxaline-2-carboxylic acid with thionyl chloride gives the acid chloride (79%), which undergoes the expected reactions.¹⁶⁶ The gas-phase pyrolysis of quinoxaline-2,3-dicarboxylic anhydride (157) over a Nichrome coil gives *o*-phthalonitrile (158) (72%), probably via 2,3-quinoxalyne (159) which ring-cleaves, and the diisocyanide subsequently rearranges thermally to the dinitrile.¹⁶⁷



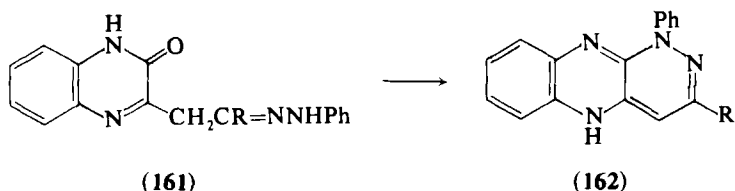
The 2,3-dicarboxylic anhydride (157) reacts with hydrazine hydrate, and the intermediate dihydrazide ring-closes to give the pyridazino[4,5-*b*]quinoxaline 160.¹⁶⁸ The isomeric pyridazino[3,4-*b*]quinoxalines (162)

¹⁶⁶ H. C. Koppel, I. L. Honigberg, R. H. Springer, and C. C. Cheng, *J. Org. Chem.* **28**, 1119 (1963).

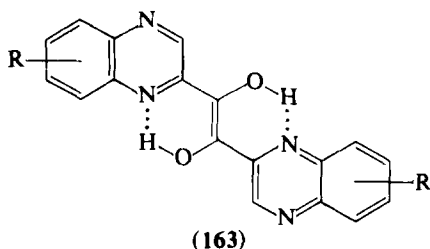
¹⁶⁷ M. P. Cava and L. Bravo, *Chem. Commun.*, 1538 (1968).

¹⁶⁸ (a) V. N. Konyukhov, T. G. Koksharova, K. V. Aglitskaya, and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin.*, 426 (1971) [*CA* **76**, 3797 (1972)]; (b) T. G. Koksharova, V. N. Konyukhov, Z. V. Pushkareva, and T. A. Pryakhina, *ibid.*, 274 (1972) [*CA* **76**, 153715 (1972)]; (c) T. G. Koksharova, L. F. Lipatova, V. N. Konyukhov, G. N. Smotrina, and Z. V. Pushkareva, *ibid.*, 556 (1973) [*CA* **79**, 32010 (1973)].

are formed by acid cyclization of quinoxalinephenylhydrazones of type **161**.¹⁶⁹



Quinoxalinecarboxaldehydes on treatment with 60% ethanolic potassium cyanide yield quinoxalins, which are thought to exist in the hydrogen-bonded tautomeric form **163**. Aerial oxidation of quinoxaloin gives quinoxalil, and oxidation with concentrated nitric acid yields quinoxaline-2-carboxylic acid.¹⁷⁰



R = 6- or 7-chloro
6- or 7-nitro

H. DERIVATIVES OF QUINOXALINE-2-THIONE AND QUINOXALINE-2,3-DITHIONE

Quinoxaline-2,3-dithione, as reported earlier,¹ is useful for its coordinating properties with transition metals. The metal complexes of the dithione with Cu, Ni, Zn, Pd, and Pt have been prepared,¹⁷¹ and the spectral properties of the Ni and Pd complexes examined.^{171,172} UV data indicate that quinoxaline-2,3-dithione (**153**) is present as such, rather than as 2,3-dimercaptoquinoxaline; the highly colored nature of its complexes is attributed to charge transfer.¹⁷¹

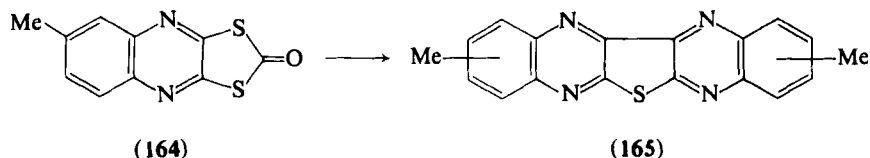
¹⁶⁹ (a) H. Dahn and H. Moll, *Helv. Chim. Acta* **49**, 2426 (1966); (b) H. Dahn and J. P. Fumeaux, *Bull. Soc. Vandoise Sci. Nat.* **70**, 313 (1970) [*CA* **75**, 140791 (1971)]; (c) Yu. S. Andreichikov, G. D. Plakhina, and R. F. Saraeva, *Khim. Tekhnol. Obl. Nauchno-Tekh. Konf. (Mater)* **4th**, 1973 (1973) **2**, 58 [*CA* **82**, 140072 (1975)].

¹⁷⁰ H. J. Binte, G. Henseke, W. Bauer, and K. Köhnke, *Z. Chem.* **8**, 104 (1968).

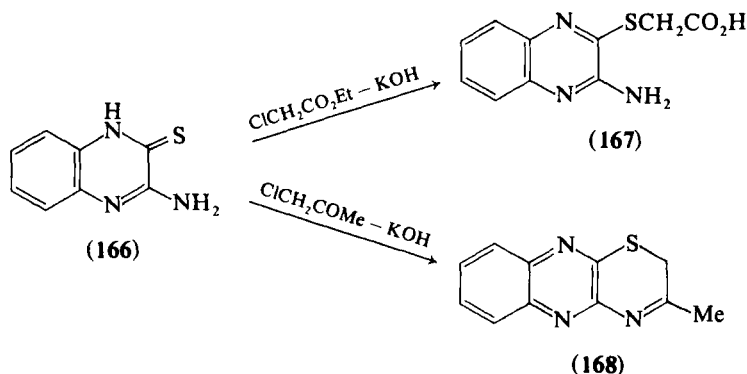
¹⁷¹ L. J. Theriot, K. K. Ganguli, S. Kavarnos, and I. Bernal, *J. Inorg. Nucl. Chem.* **31**, 3133 (1969).

¹⁷² A. T. Pilipenko, L. I. Savranskii, O. P. Ryabushko, and L. A. Krivokhizhina, *Dopov. Akad. Nauk. Ukr. RSR, Ser. B*, **36**, 447 (1974) [*CA* **81**, 62915 (1974)].

6-Methylquinoxaline cyclic dithiolcarbonate (Morestan) (**164**) is a useful pesticide. When irradiated in benzene at 280 nm, it is transformed into a dimethyl thieno[2,3-*b*:4,5-*b'*]diquinoxaline (**165**).¹⁷³



2-Aminoquinoxaline-3-thione (**166**) reacts with α -chloroesters under alkaline conditions, and (2-aminoquinoxaline)thioglycolic acids (**167**) are obtained. With α -haloketones in the presence of alkali, ring closure takes place and quinoxalino[2,3-*b*][1,4]thiazines, such as **168** are isolated.¹⁷⁴ Photolysis of 3-methylquinoxaline-2-thione in ethanol or chloroform yields 3-methyl-2-quinoxalyl disulfide.¹⁷⁵



Some reactions of 2-methylsulfonylquinoxaline (**169**) have recently been investigated by Hayashi and his co-workers.¹⁷⁶ Reaction of **169** with ketones in benzene in the presence of sodamide yields 2-(2-quinoxaliny) ketones (see Section IV,F^{149,161}); with active methylene compounds, e.g., ethyl cyanoacetate, the 2-substituted quinoxaline (**170**) is isolated.¹⁷⁶ It was also found that reaction of 2-methylsulfonyl-

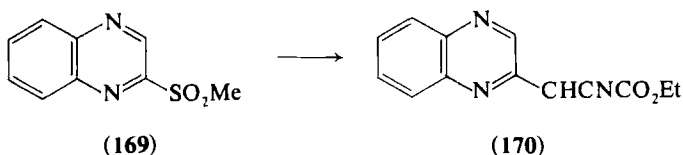
¹⁷³ W. F. Gray, J. H. Pomerantz, and R. D. Ross, *J. Heterocycl. Chem.* **9**, 707 (1972).

¹⁷⁴ (a) I. Ya. Postovskii and N. G. Koshel, *Khim. Geterotsikl. Soedin.* **7**, 853 (1971) [*CA* **76**, 25239 (1972)]; (b) U.S.S.R. Patent 317,656 (1971) [*CA* **76**, 99710 (1972)]; (c) U.S.S.R. Patent 318,579 (1971) [*CA* **76**, 46215 (1972)].

¹⁷⁵ M. Hoshino, K. Suzuki, and S. Oguchi, *Tokyo Gakugei Daigaku Kiyo, Dai-4-Bu* **27**, 134 (1975) [*CA* **84**, 120781 (1976)].

¹⁷⁶ (a) E. Hayashi and T. Miyagishima, *Yakugaku Zasshi* **87**, 826 (1967) [*CA* **67**, 116866 (1967)]; (b) **87**, 1103 (1967) [*CA* **68**, 49560 (1968)]; (c) **88**, 303 (1968) [*CA* **69**, 59199 (1968)]; (d) E. Hayashi and A. Utsunomiya, *ibid.* **95**, 774 (1975).

quinoxaline with acetophenone in dimethyl sulfoxide in the presence of potassium cyanide results in the formation of 2-phenylfuro[2,3-*b*]-quinoxaline, accompanied by 2-cyano- and 2,3-dicyanoquinoxaline.¹⁷⁶



In a series of papers, Barlin and Brown^{177–181} reported their investigations of the nucleophilic displacement reactions of 2-alkylthio-, 2-alkylsulfinyl-, and 2-alkylsulfonyl-quinoxalines. 2-Methylsulfonylquinoxaline reacts about 60 times more rapidly with methoxide ion than 2-chloroquinoxaline, owing to a lower activation energy of reaction.¹⁷⁷ 2-Methylsulfinylquinoxaline (171) is about as reactive as the methylsulfonyl compound, but 2-methylthioquinoxaline (172) is less reactive than the chloroquinoxaline.¹⁷⁹ In compounds (2-SO_nR) related to 169, 171, and 172, the ease of nucleophilic displacement by methoxide ion markedly decreases as the size of the alkyl group R increases: Me > Et > isoPr > *tert*-Bu.¹⁸¹



I. QUINOXALINES SUBSTITUTED IN THE BENZENE RING

Quinoxalines substituted in the 5- or 6-position generally follow the pattern of reactions expected for substituted benzene derivatives, although recently there have been reports of interesting and unexpected reactions with nucleophiles (see Section III,A,2 and references 85–90). 6-Methylquinoxaline is brominated in the side chain when treated with *N*-bromosuccinimide in carbon tetrachloride in the presence of azobisisobutyronitrile, to form 6-bromomethylquinoxaline.¹⁸²

¹⁷⁷ G. B. Barlin and W. V. Brown, *J. Chem. Soc. B*, 736 (1967).

¹⁷⁸ G. B. Barlin and W. V. Brown, *J. Chem. Soc. C*, 2473 (1967).

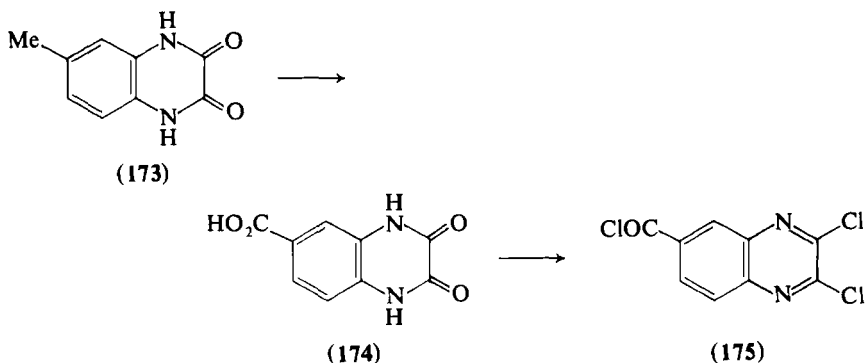
¹⁷⁹ G. B. Barlin and W. V. Brown, *J. Chem. Soc. B*, 1435 (1968).

¹⁸⁰ G. B. Barlin and W. V. Brown, *J. Chem. Soc. C*, 921 (1969).

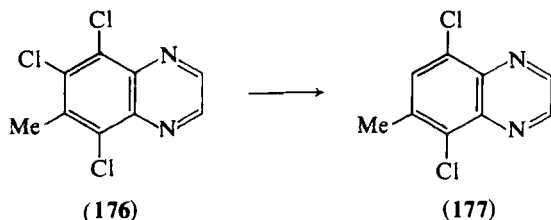
¹⁸¹ G. B. Barlin and W. V. Brown, *J. Chem. Soc. B*, 333 (1969).

¹⁸² R. C. De Selms, R. J. Greaves, and W. R. Schleigh, *J. Heterocycl. Chem.* **11**, 595 (1974).

6-Methylquinoxaline-2,3-dione (**173**) is oxidized with $\text{Co}(\text{OAc})_2$; $\text{Mn}(\text{OAc})_2$ in $\text{HBr}/\text{H}_2\text{O}$ to the 6-carboxylic acid (**174**),¹⁸³ which on treatment with thionyl chloride is converted into 2,3-dichloroquinoxaline-6-carbonyl chloride (**175**).¹⁸⁴ The 6-sulfonyl chloride is obtained from quinoxaline-2,3-dione and chlorosulfonic acid and treatment of the resulting 6-chlorosulfonyl derivative with phosphoryl chloride and pyridine.¹⁸⁵ Such derivatives are useful synthetic dye intermediates.



5,6,8-Trichloro-7-methylquinoxaline (**176**) undergoes hydrodechlorination in good yield with aqueous ethanolic potassium hydroxide, to the 5,8-dichloro compound (**177**).¹⁸⁶ A mechanism involving hydride ion transfer is proposed. 2,3-Dimethyl-5,8-dihydroxyquinoxaline (**178**) is oxidized at room temperature with silver oxide to the 5,8-dione (**179**),¹⁸⁷ which reacts with secondary amines to give 6-(*N*-substituted)amino-5,8-quinoxalinediones (e.g., **180**).¹⁸⁸ Both 2,3-



¹⁸³ Y. W. Chong, French Patent 1,386,355 (1965) [*CA* **62**, 14702 (1965)].

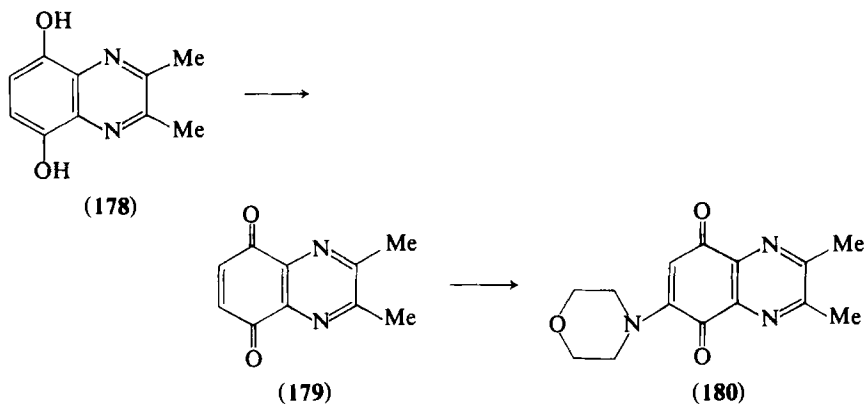
¹⁸⁴ J. PirkI and C. Fisar, Czech. Patent 116,695 (1965) [*CA* **65**, 13737 (1966)].

¹⁸⁵ J. PirkI, Czech. Patent 117,041 (1965) [*CA* **65**, 13737 (1966)].

¹⁸⁶ D. E. Burton, D. Hughes, G. T. Newbold, and J. A. Elvidge, *J. Chem. Soc. C*, 1274 (1968).

¹⁸⁷ G. A. Efimova, and L. S. Efros, *Zh. Org. Khim.* **2**, 531 (1966) [*CA* **65**, 8910 (1966)].

¹⁸⁸ K. H. Ford and M. M. Joullié, *J. Heterocycl. Chem.* **3**, 529 (1966).

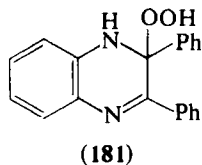


dimethyl- and 2,3-diphenyl-quinoxaline-5,8-dione participate as dienophiles in Diels–Alder reactions.¹⁸⁹

V. Reactions of Quinoxaline *N*-Oxides

The synthesis of quinoxaline *N*-oxides from benzofurazan 1-oxides, and by *N*-oxidation of the corresponding substituted quinoxaline derivatives, has already been discussed (Sections II,D and III,C, respectively).

Mager and Berends¹⁹⁰ suggest that *N,N'*-dibenzoyl-*o*-phenylenediamine is obtained as a by-product during the oxidation of 2,3-diphenylquinoxaline with hydrogen peroxide and acetic acid as a consequence of the initial formation of the hydroperoxide **181**.



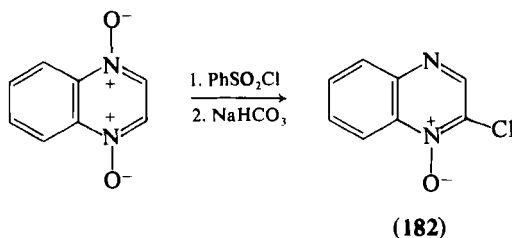
A. HALOGENATION

There are several reports of the deoxygenative halogenation of quinoxaline *N*-oxides. Thus, 3-(*o*-hydroxyphenyl)quinoxaline 1-oxide with sulfonyl chloride furnishes 2-chloro-3-(*o*-hydroxyphenyl)quinoxaline,⁵¹ and 2,3-diphenylquinoxaline 1-oxide with phosphoryl

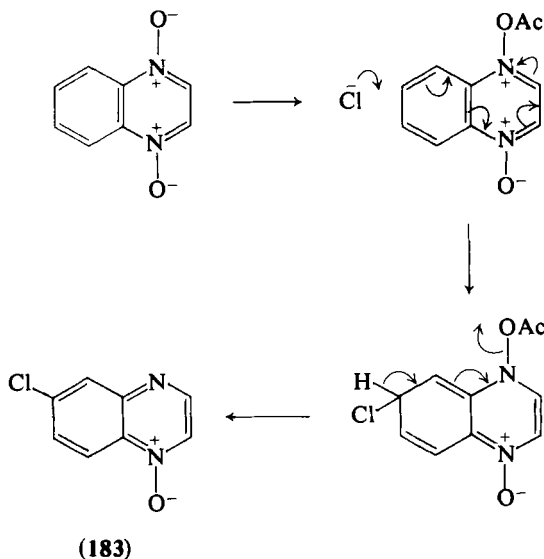
¹⁸⁹ (a) W. F. Gum and M. M. Joullie, *J. Org. Chem.* **30**, 2583 (1965); (b) G. Kumar and A. P. Bhaduri, *Indian J. Chem.* **13**, 1009 (1975).

¹⁹⁰ H. I. X. Mager and W. Berends, *Rec. Trav. Chim. Pays-Bas* **84**, 1329 (1965).

chloride gives 6-chloro-2,3-diphenylquinoxaline. Similarly, 5,7-dichloro-2,3-diphenylquinoxaline is isolated from reaction of the 1,4-dioxide and phosphoryl chloride.²² 2-Chloroquinoxaline 1-oxide (**182**) is obtained in about 70% yield by treatment of quinoxaline 1,4-dioxide with benzenesulfonyl chloride followed by neutralization of the benzenesulfonate initially formed.¹⁹¹



The 2-chloro-1-oxide is also obtained from the 1,4-dioxide by photolysis in dilute hydrochloric acid²²; however, when acetyl chloride is used, substitution in the benzene ring occurs and 6-chloroquinoxaline 1-oxide (**183**) is obtained, probably by the mechanism outlined.¹⁹²

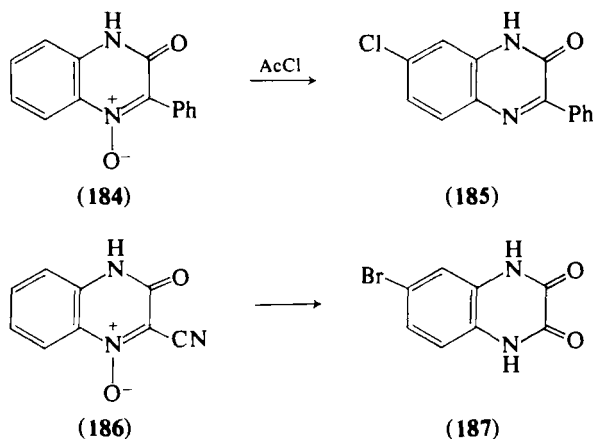


A similar reaction resulting in the formation of compound **185** is observed when 3-phenyl-2-quinoxalinone 4-oxide (**184**) is treated with

¹⁹¹ A. S. Elina, *Khim. Geterotsikl. Soedin.*, 724 (1967) [*CA* **68**, 59532 (1968)].

¹⁹² Y. Ahmad, M. S. Habib, M. I. Qureshi, and M. A. Farogi, *J. Org. Chem.* **38**, 2176 (1973).

acetyl chloride, ring substitution again being accompanied by deoxygenation.¹⁹³



6-Bromoquinoxaline-2,3-dione (187) is formed in 30% yield on treatment of 2-cyano-3-quinoxalinone 1-oxide (186) with fuming hydrobromic acid.¹⁹⁴

Chlorination of 5-hydroxyquinoxaline 1,4-dioxide in methylene chloride gives the 6,8-dichloro derivative, but reaction with *N*-chlorosuccinimide yields 8-chloro-5-hydroxyquinoxaline dioxide. Bromination in acetic acid gives the 6,8-dibromo derivative.^{195a, b} Side-chain bromination is observed, however, when 2,3-dimethylquinoxaline 1,4-dioxide reacts with bromine in dioxane; 2,3-bis(bromomethyl)quinoxaline 1,4-dioxide is formed.^{195c}

B. OXIDATION REACTIONS

2-Methylquinoxaline 1,4-dioxide (188) is converted into 2-formylquinoxaline 1,4-dioxide (190) by oxidation with selenium dioxide in refluxing benzene,¹⁹⁶ or alternatively by treatment with *p*-nitrosodi-

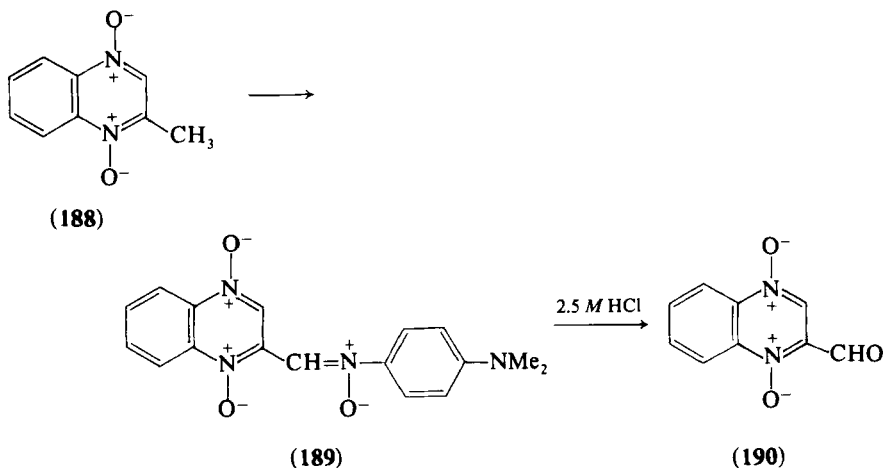
¹⁹³ Y. Ahmad, M. S. Habib, Ziauddin, and Naz Bashir, *Bull. Chem. Soc. Jpn.* **38**, 1654 (1965).

¹⁹⁴ Y. Ahmad, M. S. Habib, M. Iqbal, and Ziauddin, *Bull. Chem. Soc. Jpn.* **38**, 562 (1965).

¹⁹⁵ (a) R. H. B. Galt, U.S. Patent 3,479,354 (1969) [*CA* **72**, 79095 (1970)]; (b) R. H. B. Galt and R. J. Pearce, British Patent 1,237,438 (1971) [*CA* **75**, 103340 (1971)]; (c) A. S. Elina, L. G. Tsyruknikova, O. Yu. Magidson, and V. I. Fatneva, U.S.S.R. Patent 178,382 (1973) [*CA* **80**, 37163 (1974)].

¹⁹⁶ P. Benko, L. Buda, L. Pallos, I. Simonek, P. Foris, J. Kovacs, K. Magyar, and G. Toker, *Hug. Teljes* 8581 (1974) [*CA* **82**, 57734 (1975)].

methylaniline, via the nitron (189). The carboxaldehyde is readily oxidized with hydrogen peroxide-acetic acid at 20°–25° to 2-carboxyquinoxaline 1,4-dioxide. The latter compound is decarboxylated in acetic acid at 65°–70° to quinoxaline 1,4-dioxide.¹⁹⁷



When 2-carboxyquinoxaline 1,4-dioxide is treated with NH₃ in anhydrous dimethylformamide (DMF), in the presence of *N,N'*-carbonyldiimidazole, 2-carbamoylquinoxaline 1,4-dioxide is obtained.¹⁹⁸

Oxidation of 2-methyl-3-(methylthio)quinoxaline 1,4-dioxide with 1 equivalent of *m*-chloroperbenzoic acid yields the corresponding sulfoxide, and 2 equivalents of oxidizing agent gives the sulfone, both products being isolated in good yield. Treatment of the substituted sulfoxide- or sulfone-quinoxaline dioxides with aqueous halogen acids leads to nucleophilic displacement and the formation of 2-haloquinoxaline 1,4-dioxides.¹⁹⁹

C. NUCLEOPHILIC SUBSTITUTION REACTIONS

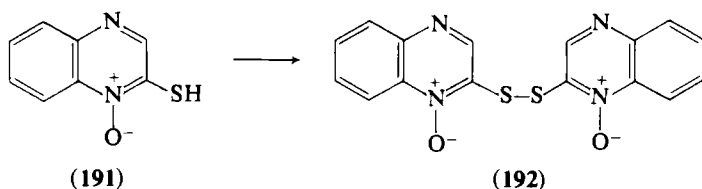
Quinoxaline *N*-oxides substituted in the 2,3-position undergo facile nucleophilic displacement. Numerous reactions have been investigated in the search to prepare derivatives which are active

¹⁹⁷ A. S. Elina, L. G. Tsyruhnikova, and I. S. Musatova, *Khim.-Farm. Zh.* 1, 10 (1967) [*CA* 68, 78247 (1968)].

¹⁹⁸ Societe des Usines Chimiques Rhone-Poulenc, Fr.M. 3717 (1966) [*CA* 66, 95087 (1967)].

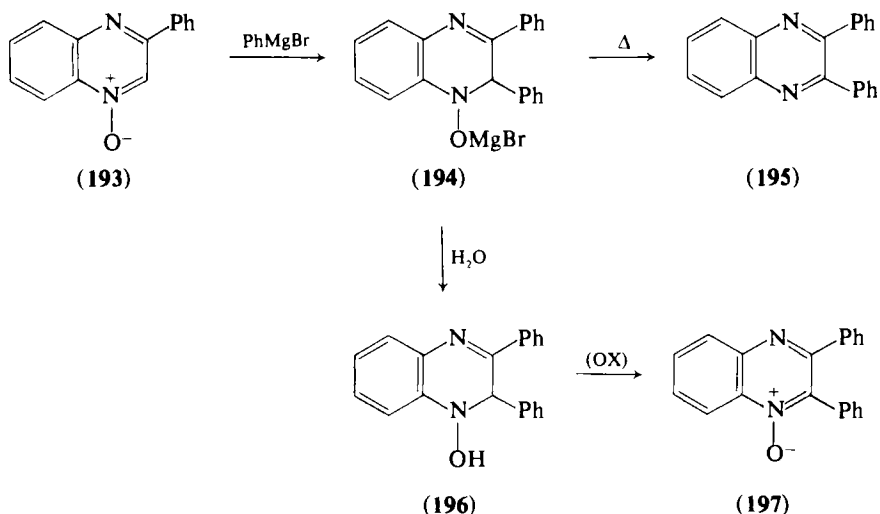
¹⁹⁹ E. Abushanab, *J. Org. Chem.* 38, 3105 (1973).

pharmacologically.^{191,200–204} Elina examined the nucleophilic displacement reactions of 2-chloroquinoxaline 1-oxide and found that these reactions take place much more readily than with 2-chloroquinoxaline itself (Cheeseman and Torzs²²). Reaction with NaOH yields the 2-hydroxy and with NH₄OH the 2-amino 1-oxides. Treatment with potassium cyanide gave a small amount of the 2-cyano-1-oxide, together with some 2-carbamoylquinoxaline 1-oxide.²⁰¹



2-Mercaptoquinoxaline 1-oxide (191) (obtained from reaction of 2-chloroquinoxaline 1-oxide with NaSH) on oxidation with oxygen forms the corresponding disulfide (192).²⁰³

The reactions of 2-phenylquinoxaline 4-oxide (193) with Grignard reagents give two main products, e.g., 2,3-diphenylquinoxaline (195)



²⁰⁰ A. S. Elina, *Khim. Geterotsikl. Soedin.*, 940 (1967) [*CA* **68**, 114549 (1968)].

²⁰¹ A. S. Elina and L. G. Tsyrlinikova, *Khim.-Farm. Zh.* **1**, 36 (1967) [*CA* **69**, 27384 (1968)].

²⁰² A. S. Elina, *Zh. Obshch. Khim.* **34**, 2809 (1964) [*CA* **61**, 14673 (1964)].

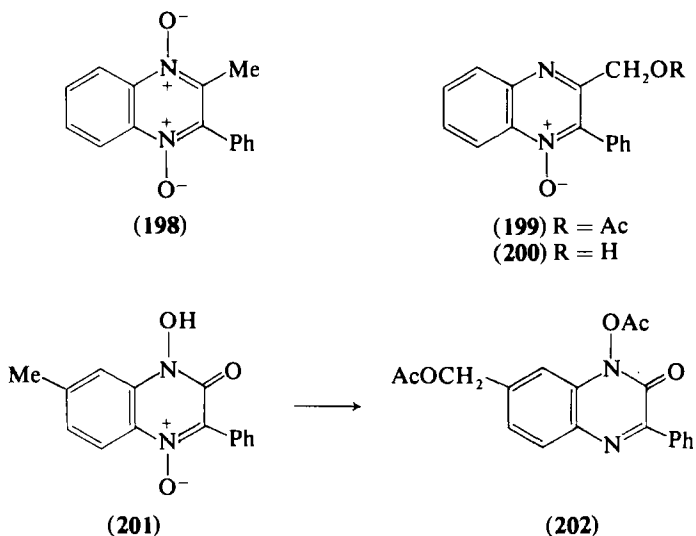
²⁰³ M. L. Douglass, U.S. Patent 3,733,323 (1973) [*CA* **79**, 42557 (1973)].

²⁰⁴ J. M. Cox, R. T. V. Fox, and R. A. Burrell, Ger. Offen. 2,362,591 (1974); *CA* **81**, 105563 (1974)].

and 2,3-diphenylquinoxaline 1-oxide (**197**), which are rationalized via the intermediates **194** and **196**.²⁰⁵

Elina and co-workers have extensively investigated the reactions of 2-methylquinoxaline 1,4-dioxide and 2,3-dimethylquinoxaline 1,4-dioxide with aldehydes.²⁰⁶ Under alkaline conditions formalin gives hydroxyethyl derivatives, and aryl aldehydes form styrylquinoxalines. As expected, 2,3-dimethylquinoxaline 1-oxide yields 3-methyl-2-styrylquinoxaline 1-oxide.²⁰⁷

Treatment of 2,3-dimethylquinoxaline dioxides and monoxides with acetic anhydride yield 2,3-bis(acetoxymethyl)quinoxalines and 2-acetoxymethylquinoxalines, respectively.^{112,208} Under alkaline conditions these derivatives are hydrolyzed to the corresponding hydroxymethylquinoxalines. Thus, 2-methyl-3-phenylquinoxaline-1,4-dioxide



²⁰⁵ E. Hayashi and C. Iijima, *Yakugaku Zasshi* **86**, 571 (1966) [CA **65**, 15375 (1966)].

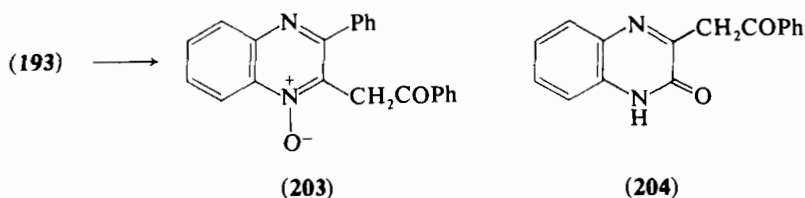
²⁰⁶ (a) A. S. Elina and L. G. Tsyrlnikova, *Zh. Obshch. Khim.* **34**, 2077 (1964) [CA **61**, 8308 (1964)]; (b) U.S.S.R. Patent 162,148 (1964) [CA **61**, 1069 (1964)]; (c) *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR*, 432 (1966) [CA **65**, 13704, (1966)], (d) 272 (1966) [CA **65**, 3873 (1966)].

²⁰⁷ N. E. Plevachuk and S. N. Baranov, *Khim. Geterotsikl. Soedin.* **4**, 729 (1968) [CA **70**, 3778, (1969)].

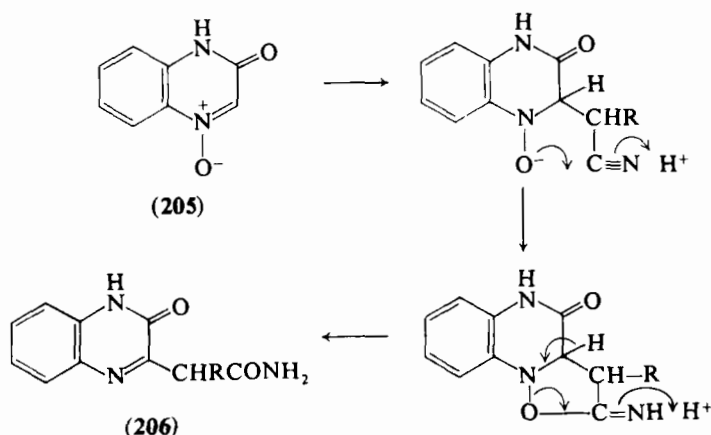
²⁰⁸ (a) A. S. Elina, U.S.S.R. Patent 136,379 (1960) [CA **59**, 28356 (1963)]; (b) *Khim. Geterotsikl. Soedin.*, 545 (1968) [CA **69**, 96660 (1968)]; (c) A. S. Elina, L. G. Tsyrlnikova, and O. Yu. Magidson, U.S.S.R. Patent 207,917 (1967) [CA **69**, 52180 (1968)]; (d) A. S. Elina, I. S. Musatova, and L. G. Tsyrlnikova, *Khim.-Farm. Zh.* **5**, 6 (1971) [CA **75**, 151759 (1971)]; (e) A. S. Elina, L. G. Tsyrlnikova, and G. D. Syrova, *Khim. Geterotsikl. Soedin.*, 149 (1969) [CA **71**, 13093 (1969)].

(198) yields **199**, hydrolyzed (NaHCO_3) to **200**.¹¹² Interestingly, 1-hydroxy-7-methyl-2(1*H*)-quinoxalinone 4-oxide (**201**) with refluxing acetic anhydride gives the 7-acetoxymethylquinoxalinone (**202**) (85%).²⁰⁹

Hayashi and his co-workers investigated the reactions of 2-substituted quinoxaline 4-oxides with ketones.^{210–212} 2-Phenylquinoxaline 4-oxide (**193**) yields 2-phenyl-3-phenacylquinoxaline 4-oxide (**203**) with acetophenone and sodamide. However, 2-cyanoquinoxaline 4-oxide under these conditions yields ω -(3,4-dihydro-3-oxo-2-quinoxaliny)acetophenone (**204**) by displacement of the cyano group by the ketone carbanion and rearrangement of the *N*-oxide.²¹²



When 2-quinoxalinone 4-oxide (**205**) is treated with cyanides of the type RCH_2CN ($\text{R} = \text{CO}_2\text{Et}$ or CN) in the presence of piperidine, an interesting rearrangement of the intermediate quinoxalinone takes place, via intramolecular nucleophilic attack of the *N*-oxide oxygen on the cyanide group forming **206**.²¹³



²⁰⁹ J. C. Mason and G. Tennant, *Chem. Commun.*, 1550 (1971).

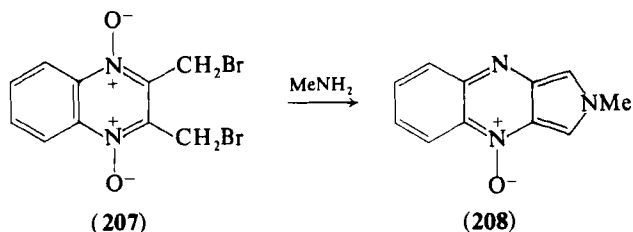
²¹⁰ C. Iijima and E. Hayashi, *Yakugaku Zasshi* **92**, 736 (1972) [*CA* **77**, 75190 (1972)].

²¹¹ C. Iijima and E. Hayashi, *Yakugaku Zasshi* **91**, 721 (1971) [*CA* **75**, 129758 (1971)].

²¹² E. Hayashi and S. Suzuki, *Yakugaku Zasshi* **94**, 878 (1974) [*CA* **81**, 152156 (1974)].

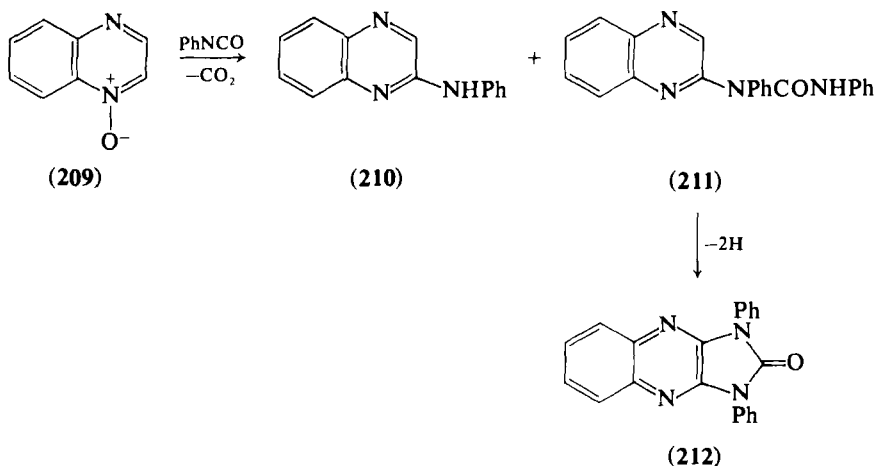
²¹³ G. Tennant, *Chem. Ind. (London)*, 1622 (1964).

2,3-Bis(bromomethyl)quinoxaline 1,4-dioxide (**207**) with liquid methylamine gives the pyrroloquinoxaline *N*-oxide (**208**) in excellent yield, which can be deoxygenated by either phosphorus trichloride or Raney nickel to a stable diazaaisoindole.²¹⁴



D. CYCLOADDITIONS AND REARRANGEMENTS

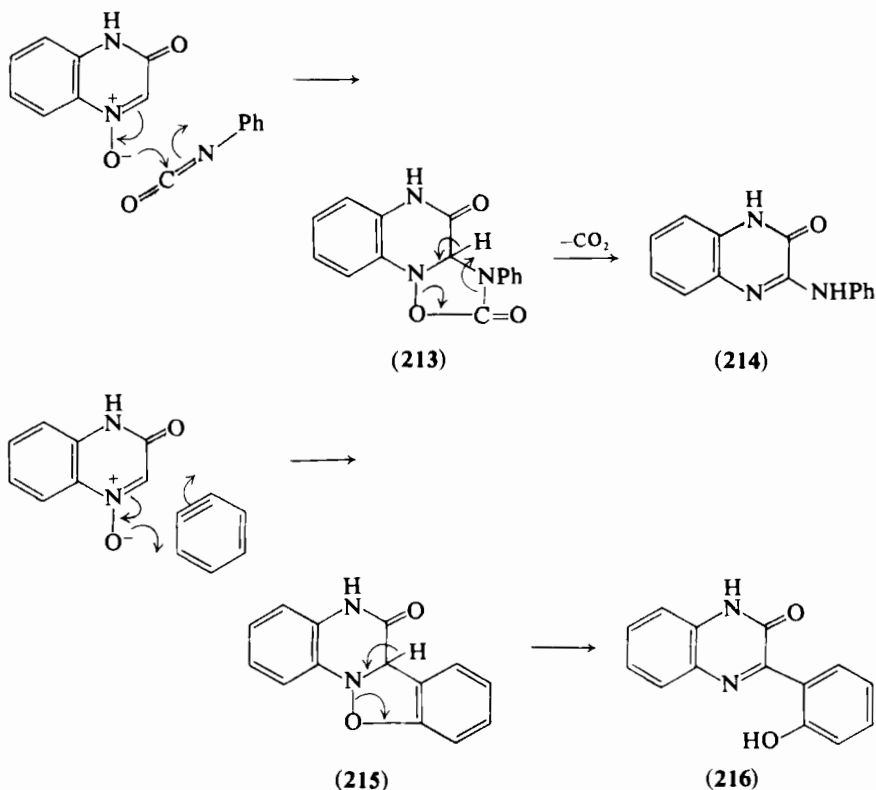
Quinoxaline 1-oxide (**209**) reacts with phenyl isocyanate to give 2-anilinoquinoxaline (**210**) together with 1,3-diphenyl-1-(2-quinoxaliny)-urea (**211**) and cyclized oxidation product of the urea **212**.²¹⁵ 2-Quinoxalinone 4-oxide (**205**) and its 1-methyl derivative undergo addition reactions, e.g., with phenyl isocyanate and benzyne to give compounds **214** and **216**, respectively.²¹⁶ These reactions are formulated as proceeding via the intermediate cycloadducts **213** and **215**. Compound **216** has also been obtained by photolysis of 3-(*o*-hydroxyphenyl)quinoxaline 1-oxide.⁵¹ 1,3-Dipolar cycloaddition of quinoxaline



²¹⁴ R. C. Anderson and R. H. Fleming, *Tetrahedron Lett.*, 1581 (1969).

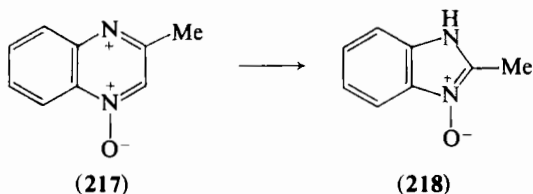
²¹⁵ C. Iijima, *Yakugaku Zasshi* **87**, 164 (1967) [*CA* **67**, 3067 (1967)].

²¹⁶ J. C. Mason and G. Tennant, *Chem. Commun.*, 218 (1972).



mono- and dioxides with *N*-phenylmaleimide, or dimethyl acetylenedicarboxylate have also been reported.²¹⁷

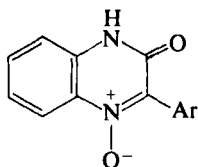
Quinoxaline *N*-oxides undergo various rearrangements. Ring contraction to benzimidazoles is exemplified by 2-methylquinoxaline 4-oxide (217) which on warming with 30% hydrogen peroxide in methanolic potassium hydroxide yields 37% of 2-methylbenzimidazole 3-oxide (218).²¹⁸



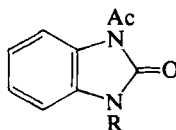
²¹⁷ M. Ungureanu, I. Druta, and I. Zugravescu, *An. Stiint. Univ. "A.I. Cuza" Iasi, Sect. Ic* **20**, 29 (1974) [*CA* **82**, 125351 (1975)].

²¹⁸ E. Hayashi and Y. Miura, *Yakugaku Zasshi* **87**, 648 (1967) [*CA* **67**, 90775 (1967)].

Habib and co-workers observed the rearrangement of 2-quinoxalinone 4-oxides (**219**) on treatment with acetic anhydride to 1,3-diacetyl- or 1-acetyl-3-acyl-2-benzimidazolones (**220**).²¹⁹ Recently, the ring contraction of 2-azidoquinoxaline 1-oxide to 2-cyano-1-hydroxybenzimidazole has been reported.²²⁰



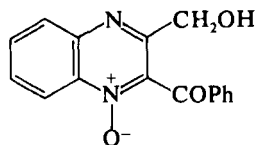
(219)



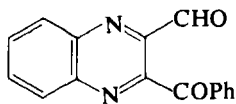
(220)

R = COAr or Ac

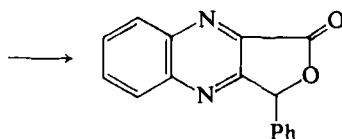
The lactone **223** was isolated from 2-benzoyl-3-hydroxymethylquinoxaline 1-oxide **221** on treatment with alkali and subsequent acidification, probably by intramolecular Cannizzaro reaction of 2-benzoyl-3-quinoxaline carboxyaldehyde (**222**), which in turn is obtained from **221** by a series of tautomeric shifts and 1,4-elimination.²²¹



(221)



(222)



(223)

E. REDUCTION

Quinoxaline *N*-oxides are deoxygenated by phosphorus trichloride in chloroform,²²² sodium dithionite in ethanol or acetic acid,^{194, 221, 223} zinc

²¹⁹ Y. Ahmad, M. S. Habib, A. Mohammady, B. Bakhtiari, and S. A. Shamsi, *J. Org. Chem.* **33**, 201 (1968).

²²⁰ R. A. Abramovitch and B. W. Cue, *Heterocycles* **1**, 227 (1973).

²²¹ M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 4609 (1968).

²²² T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 2319 (1964).

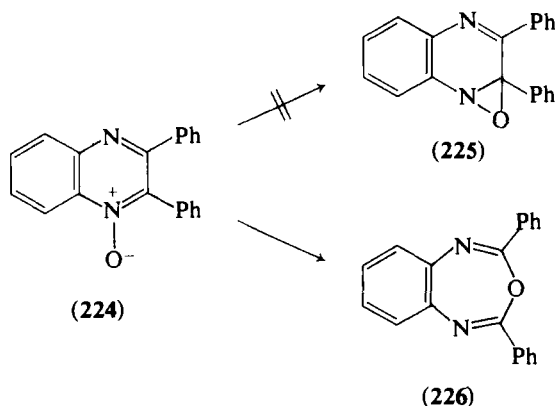
²²³ M. J. Haddadin, G. E. Zahr, T. N. Rawdah, N. C. Chelhot, and C. H. Issidorides, *Tetrahedron* **30**, 659 (1974).

and hydrochloric acid,¹⁹⁴ catalytic hydrogenation over palladium-charcoal,^{22,194} and sodium borohydride.²²⁴ Reduction of 2,3-disubstituted quinoxaline 1,4-dioxides with sodium borohydride gave predominantly *cis*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines,²²⁴ while deoxygenation first to the corresponding quinoxalines with sodium dithionite, followed by reduction with metallic sodium gave predominantly the *trans* compounds.²²⁴

Reduction of 2-cyano-3-quinoxalinone 1-oxide with sodium dithionite, zinc and acetic acid, or by catalytic hydrogenation was accompanied by loss of the cyano group, and in each case 2-quinoxalinone was formed.¹⁹⁴

F. PHOTOCHEMICAL REACTIONS

Quinoxaline *N*-oxides undergo rearrangements when UV-irradiated. 2,3-Diphenylquinoxaline 1-oxide (**224**) was originally thought to rearrange to the oxazirino[2,3-*a*]quinoxaline (**225**).²²⁵ However, subsequently the product was found to be 2,4-diphenyl-3,1,5-benzoxadiazepine (**226**).²²⁶ This reassignment was supported by NMR spectroscopy, and oxadiazepine formation on irradiation of 2,3-bis(4-bromophenyl)quinoxaline 1-oxide was confirmed by X-ray crystallography.²²⁷



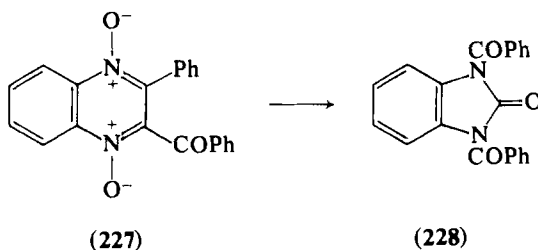
²²⁴ M. J. Haddadin, H. N. Alkaysi, and S. E. Saheb, *Tetrahedron* **26**, 115 (1970).

²²⁵ (a) C. Kaneko, I. Yokoe, S. Yamada, and M. Ishikawa, *Chem. Pharm. Bull.* **14**, 1316 (1966); (b) A. Kubo, S. Sakai, S. Yamada, I. Yokoe, C. Kaneko, A. Tatematsu, H. Yoshizumi, E. Hayashi, and H. Nakata, *Chem. Pharm. Bull.* **15**, 1079 (1967); (c) C. Kaneko, S. Yamada, and I. Yokoe, *Iyo Kinzai Kenkyusho Hokoku* **1**, 1 (1967); [*CA* **68**, 104845 (1968)]; (d) C. Kaneko, S. Yamada, I. Yokoe, and M. Ishikawa, *Tetrahedron Lett.*, 1873 (1967).

²²⁶ O. Buchardt and J. Feeney, *Acta Chem. Scand.* **21**, 1399 (1967).

²²⁷ O. Buchardt and B. Jensen, *Acta Chem. Scand.* **22**, 877 (1968).

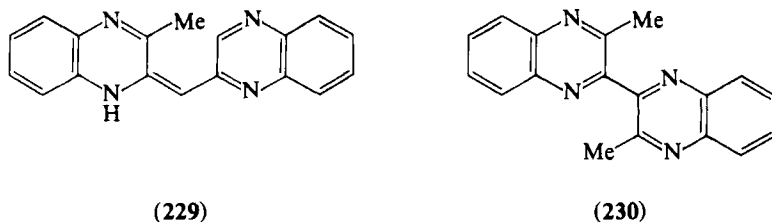
Direct-sunlight photolysis of 2-benzoyl-3-phenylquinoxaline 1,4-dioxide (**227**) yields the ring-contracted product, 1,3-dibenzoyl-2-benzimidazolone (**228**) (70%).^{53,228}



VI. Miscellaneous Quinoxaline Derivatives

A. REFORMULATION OF METHYLQUINOXALINE ORANGE

2-Methylquinoxaline on (a) treatment with hot dilute hydrochloric acid²²⁹ or (b) heating at 200° in the presence of a palladium-on-carbon catalyst,²³⁰ is converted into a high-melting orange crystalline solid, previously assigned structures **229** and **230**. Cheeseman and Tuck⁹ found that the same product was obtained from both reactions, and it was shown spectroscopically (NMR, MS) to be 6-methylpyrrolo[1,2-*a*:4,5-*b'*]diquinoxaline (**4**), also obtained by heating 2,3-dimethylquinoxaline and 2-chloroquinoxaline at 100° in the presence of HCl. This reaction is fairly general, since analogous pentacyclic derivatives have been prepared from 2-chloroquinoxaline and a variety of 3-substituted 2-methylquinoxalines,²³¹ 4-methylquinazolines, and 1-methylphthalazines.²³²



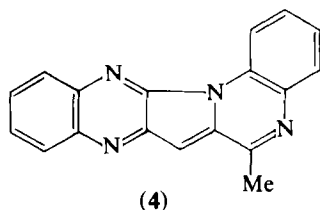
²²⁸ M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 753 (1967).

²²⁹ C. L. Leese and H. N. Rydon, *J. Chem. Soc.*, 303 (1955).

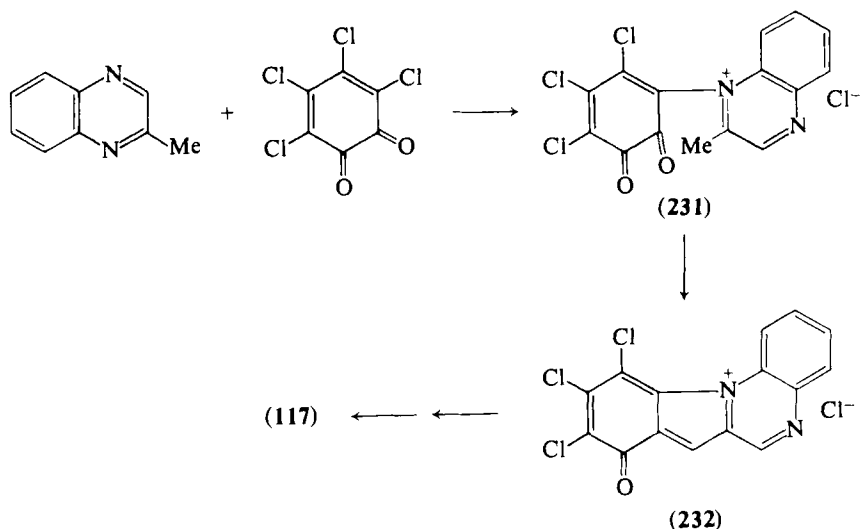
²³⁰ H. Smith-Broadbent and R. C. Anderson, *J. Org. Chem.* **27**, 2679 (1962).

²³¹ R. K. Anderson, Ph.D. Thesis, Univ. of London, 1971.

²³² S. D. Carter, Ph.D. Thesis, Univ. of London, 1975.



2-Methylquinoxaline also undergoes a novel cycloaddition reaction with two equivalents of tetrachloro-1,2-benzoquinone¹²⁹ (see Section III,A) with formation of a quinoxaline-orange type product. The reaction probably proceeds by initial formation of the quaternary salt **231** which by elimination of HCl, followed by protonation and dehydration, leads to the cyclized product **232**. This on reaction with a further equivalent of tetrachloro-1,2-benzoquinone at the C=N function gives the final yellow compound **117**.



B. QUINOXALINE GLYCOSIDES

Quinoxaline glycosides have been prepared from 2-quinoxalinone and its 3-methyl derivative and from 2-quinoxalinethione and its 3-methyl derivative.^{233–237}

²³³ W. Pfeleiderer, R. Lohrmann, F. Reisser, and D. Soell, *Pteridine Chem., Proc. Int. Symp., 3rd*, 87 (1962).

²³⁴ F. Reissert and W. Pfeleiderer, *Chem. Ber.* **99**, 547 (1966).

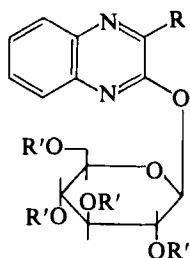
²³⁵ W. Pfeleiderer and M. Schraner, *Chem. Ber.* **104**, 1915 (1971).

²³⁶ G. Wagner and H. Frenzel, *Z. Chem.* **5**, 104 (1965).

²³⁷ G. Wagner and H. Frenzel, *Arch. Pharm.* **300**, 433 (1967).

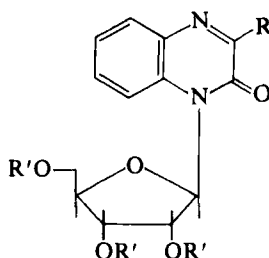
Thus, when the silver salt of 2-quinoxalinone is condensed with tetra-*O*-acetyl- α -D-glucopyranosyl bromide in xylene, the 2-glucosyl-quinoxaline (**233**: R = H; R' = Ac) is isolated. The latter compound is readily deacetylated to the glucoside (**233**: R = R' = H). During the reaction only the 2-*O*-substituted derivative is formed (steric factors probably inhibit *N*-glucosidation), and only the β -D-anomers are obtained.²³⁴

1- β -D-Ribofuranosyl-2-quinoxalinones (**234**: R = H or Me; R' = H) have been synthesized by silylation of the 2-quinoxalinone with hexamethyldisilazane, followed by condensation of the 2-trimethylsilyloxy-quinoxaline with either (a) 1-bromo-2,3,5-tri-*O*-benzoylribofuranose in benzene in the presence of mercury(II) oxide and bromide or (b) 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose in acetonitrile in the presence of tin(IV) chloride. Compounds **234**, R = H or Me, R' = C₆H₅, are readily debenzoylated with methanolic sodium methoxide to give **234**, R = H or Me, R' = H.²³⁵



(233)

R = H or Me
R' = H or Ac



(234)

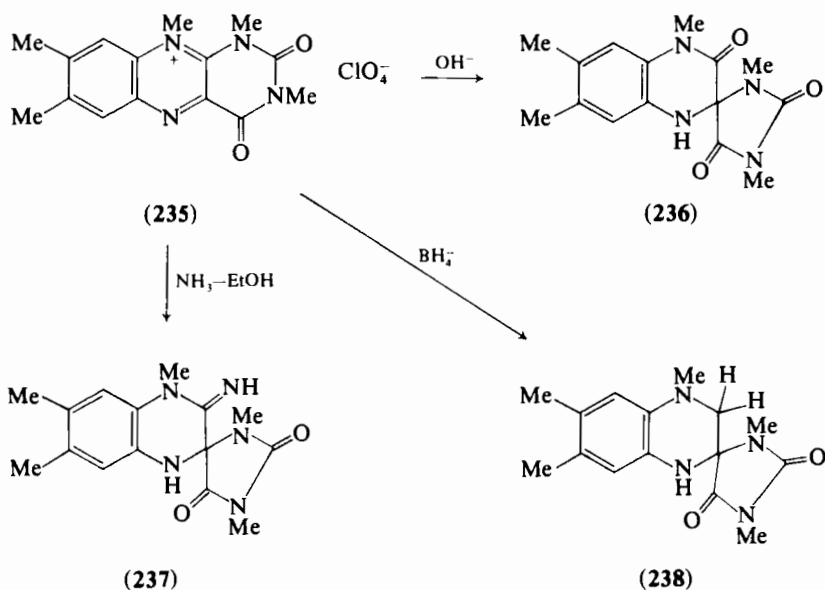
R = H or Me
R' = H or C₆H₅

C. QUINOXALINE SPIRANS

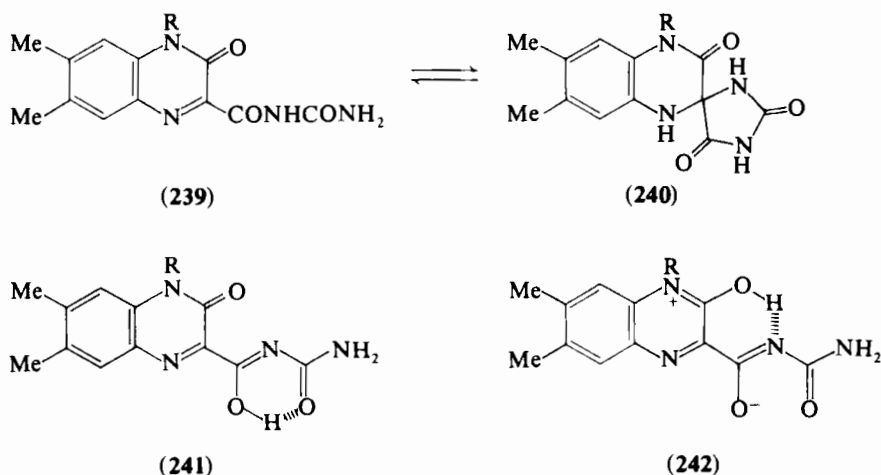
In the light of recent work of Clark-Lewis on the condensation of alloxan with *o*-aminodimethylaminobenzene²⁸⁻³⁰ and with *N*-substituted diaminobenzenes (see Section II,A), other workers have reinvestigated related reactions and reformulated the products as spiro-quinoxaline derivatives. 1,3,10-Trialkylflavinium salts (e.g., **235**) with nucleophiles, e.g., hydroxide ion, ammonia, or borohydride, yield the spiro-imidazolidinequinoxaline derivatives **236**, **237**, and **238**.²³⁸

Compounds of type **240** have been obtained by cyclization of the ureides **239**. NMR and IR show that the ureides possess strongly

²³⁸ K. H. Dudley and P. Hemmerick, *J. Org. Chem.* **32**, 3049 (1967).

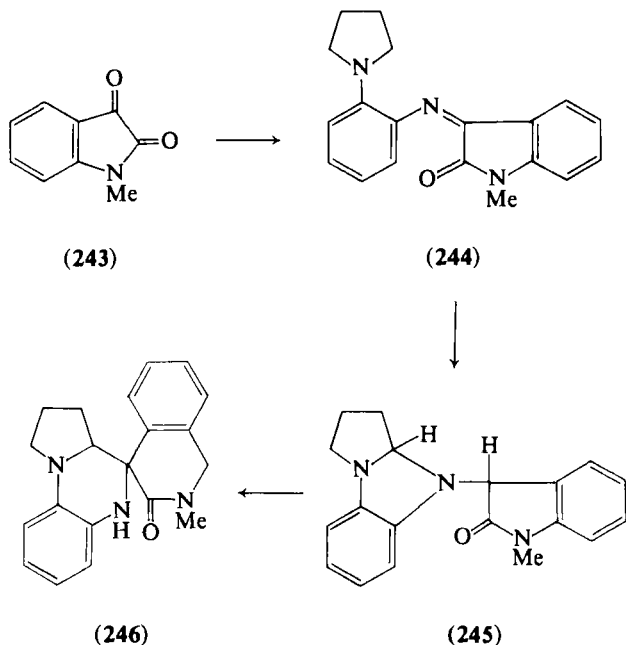


hydrogen-bonded OH bands, suggesting that tautomers **241** or **242** are probably the chief contributors.



Anils such as **244** are converted into spiroquinoxalines via dihydrobenzimidazole intermediates. *N*-Methylsatin (**243**) reacts with *o*-pyrrolidinoaniline, initially to form a purple solution of the anil **244**, from which white crystals of dihydrobenzimidazole **245** can be isolated. This on treatment with acid rearranges to the spiroquinoxaline **246**.³¹

(cf. the rearrangement **23** \rightarrow **21**, described earlier). This unusual cyclization bears a superficial resemblance to the Stevens rearrangement, in that the formation of **246** requires the presence of an acidic hydrogen in **245** (the hydrogen adjacent to C=O, and the aromatic ring).



Spiro tetrahydroquinoxaline-2,2'-[1]benzopyran (**247**) has been obtained from 1,2,4-trimethyl-3-oxo-3,4-dihydroquinoxalinium methosulfate with salicylaldehyde.²³⁹

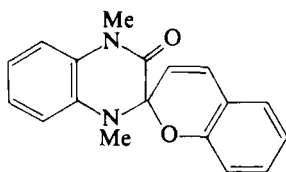
D. STEROIDAL DERIVATIVES

Steroid al quinoxalines of the type **248** have been synthesized,²⁴⁰ and the quinoxaline ring has also been incorporated into the C and D ring of steroids to give 11,14-diazaestrupentaenes (e.g., **249**).²⁴¹

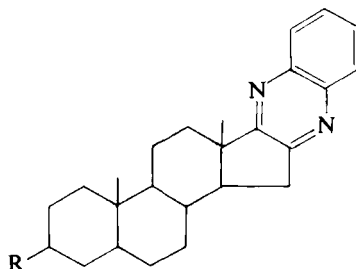
²³⁹ A. Oberlinner, H. Baumann, and K. Grychtol, Ger. Offen. 2,230,225 (1974) [*CA* **80**, 83061 (1974)].

²⁴⁰ P. Catsoulacos, *J. Heterocycl. Chem.* **10**, 933 (1973).

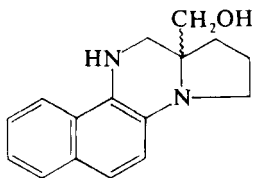
²⁴¹ V. Nacci, G. Stefancich, G. Filacchioni, R. Giuliano, and M. Artico, *Farmaco, Ed. Sci.* **28**, 49 (1973) [*CA* **78**, 84634 (1973)].



(247)



(248)

R = OH, OAc (α or β)

(249)

VII. Physical Properties

A. IONIZATION PROPERTIES

The basicities of C-5 and C-6 substituted 2,3-dimethylquinoxalines have been determined spectrophotometrically (see Table II).²⁴²

TABLE II
IONIZATION CONSTANTS OF 2,3-DIMETHYLQUINOXALINES

Substituent	pK_a	Substituent	pK_a
5-Me	2.46	6-Me	2.41
5-Br	2.16	6-Br	2.02
5-MeO	2.09	6-MeO	2.45
5-Cl	0.96	6-Cl	1.29
5-NO ₂	0.12	6-NO ₂	0.07
		6-COOH	1.05
		6-F	1.48
		6-I	1.34
		6-CN	0.41

²⁴² (a) P. Vetesnik, V. Beranek, and J. Kavalek, *Sb. Ved. Pr., Vys. Sk. Chem.-Technol., Pardubice* **14**, 37 (1966) [*CA* **67**, 63617 (1967)]; (b) P. Vetesnik, *Collect. Czech. Chem. Commun.* **33**, 556 (1968); (c) P. Vetesnik, J. Kavalek, V. Beranek, and O. Exner, *ibid.* **33**, 566 (1968).

2,3-Dimethylquinoxaline has a pK_a of 2.08, and thus in general +M-substituents at the 6-position are found to increase basicity, and -M-substituents have the reverse effect. The basicities of a series of 2,3-disubstituted quinoxalines have also been determined by potentiometric titration.²⁴³

The ionization constants of the diprotonated forms of 6-substituted 2,3-dimethylquinoxalines have been measured spectrophotometrically, 2,3-dimethylquinoxaline itself has a second pK_a value of -3.84.²⁴⁴

Molecular orbital calculations on 5-hydroxyquinoxaline indicate that the electron densities of the two nitrogen atoms are unequal, N-4 carrying a greater share of charge than N-1.²⁴⁵

The acid strengths of the quinoxaline monocarboxylic acids can be correlated with the electron densities at the carbon atoms attached to the carboxyl group. Quinoxaline 2-carboxylic acid has a pK_a of 2.88, compared with 4.03 and 3.64 for the 5- and 6-carboxylic acids. The calculated π -electron densities at C-2, C-5 and C-6 in the parent heterocycle are 0.866, 0.938, and 0.933, and thus the carboxyl group attached to C-2, the ring carbon that carries least electronic charge, is the most easily ionized.²⁴⁶

B. ULTRAVIOLET ABSORPTION SPECTRA

The electronic spectra of quinoxaline and its 2-chloro, 2-methoxy, and 2-amino derivatives have been calculated by the Pariser-Parr-Pople method. The calculated and the observed spectra agree well.²⁴⁷

Analysis²⁴⁸ of the UV spectra of the monoprotonated 2-substituted quinoxalines, and the Hammett correlation of the pK_a shifts with the substituent constants, give two straight lines, corresponding to two sets of substituents, and so reflecting a change in the position of protonation. Thus, 2-methoxyquinoxaline was found to protonate at N-4, and 2-aminoquinoxaline at N-1. However, the site of protonation of 2-chloroquinoxaline was ambiguous.

The UV spectra of substituted quinoxaline *N*-oxides **250** have been calculated and also observed experimentally,²⁴⁹ and the effect of solvent

²⁴³ J. H. Markgraf and R. J. Katl, *J. Org. Chem.* **37**, 717 (1972).

²⁴⁴ P. Vetesnik, J. Kavalek, and V. Beranek, *Collect. Czech. Chem. Commun.* **36**, 2486 (1971).

²⁴⁵ M. R. Chakrabarty, E. S. Hanrahan, and A. R. Lepley, *Tetrahedron* **23**, 2879 (1967).

²⁴⁶ W. F. Gum and M. M. Joullié, *J. Org. Chem.* **30**, 3982 (1965).

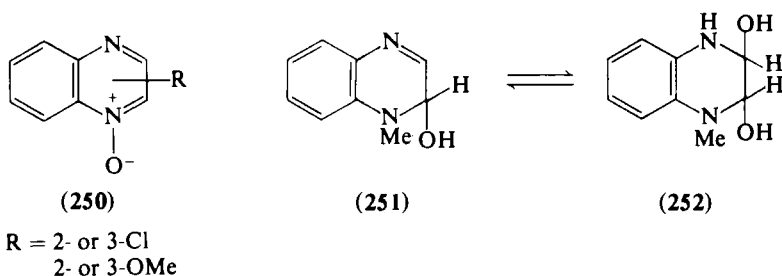
²⁴⁷ M. M. Kaganskii, I. V. Sokolova, V. I. Danilova, and G. G. Dvoryantseva, *Ural. Konf. Spektrosk.*, 7th 2, 70 (1971) [*CA* **78**, 57188 (1973)].

²⁴⁸ M. M. Kaganskii, G. G. Dvoryantseva, and A. S. Elina, *Khim. Geterotsikl. Soedin.*, 398 (1973) [*CA* **78**, 147185 (1973)].

²⁴⁹ M. M. Kaganskii, G. G. Dvoryantseva, I. V. Sokolova, and V. I. Danilova, *Khim. Geterotsikl. Soedin.*, 118 (1975) [*CA* **82**, 111182 (1975)].

on the spectra of 2-amino-, 3-amino-, 2-methoxycarbonyl-, and 3-ethoxycarbonyl-quinoxaline 1-oxide has been studied. As with pyrazine 1-oxides, the site of protonation was found to be the unoxidized N-4 atom.²⁵⁰

The UV spectrum of 1-methylquinoxalium iodide in dilute aqueous alkali at pH 10.5 shows absorption maxima at 301 and 340 nm, and in methanolic sodium methoxide, maxima at 304 and 344 nm. The two maxima in aqueous alkali are attributed to the existence of an equilibrium mixture of the pseudobase **251** and the tetrahydroquinoxaline **252**. The pseudobase is the species that gives rise to the longer wavelength absorption maximum at 340 nm. It is formed by nucleophilic attack of hydroxide ion at C-2 in aqueous alkali, and the tetrahydroquinoxaline is the result of covalent addition of water across the C3-N4 double bond of the pseudobase.²⁵¹ A similar explanation is advanced for the two maxima observed in methanol with methoxide.



The fluorescence spectra of quinoxalin-2-one and 3-substituted quinoxalin-2-ones have been reported and correlated with the absorption spectra.^{252, 253}

The π - π^* triplet of quinoxaline has been observed in a single crystal in durene, and the fine structure was found to be practically identical to that of the triplet state of naphthalene.²⁵⁴

C. NUCLEAR MAGNETIC RESONANCE SPECTRA

NMR spectroscopy has become an indispensable tool for synthetic chemists, and an additional and very useful technique for examining tautomeric and conformational equilibria.

²⁵⁰ G. G. Dvoryantseva, M. M. Kaganskii, I. S. Musatova, and A. S. Elina, *Khim. Geterotsikl. Soedin.*, 1554 (1974) [*CA* **82**, 72296 (1975)].

²⁵¹ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **50**, 917 (1972).

²⁵² I. Kumashiro, *Nippon Kagaku Zasshi* **82**, 1224 (1961) [*CA* **58**, 4047 (1963)].

²⁵³ I. Kumashiro, *Nippon Kagaku Zasshi* **82**, 1386 (1961) [*CA* **59**, 2608 (1963)].

²⁵⁴ J. S. Vincent and A. H. Maki, *J. Chem. Phys.* **39**, 3088 (1963).

The ^1H NMR spectrum of quinoxaline has been measured in carbon tetrachloride and in acetone. The signal for H-2 and H-3 appears at τ 1.27 in carbon tetrachloride, and the computed chemical shifts for H-5 (8) and H-6 (7) are at 1.97 τ and 2.33 τ , respectively.²⁵⁵

The ^1H NMR spectra of a number of 2-, 5- and 6-monosubstituted quinoxalines have also been analyzed and their chemical shifts and coupling constants reported. In these compounds J_{23} is 1.7–1.9 Hz; J_{67} 5.0–8.3 Hz; J_{78} 8.4–10.3 Hz; J_{57} 1.4–2.7 Hz; J_{68} 0.7–2.9 Hz; and J_{58} 0.3–0.8 Hz.²⁵⁶ The very small value for J_{23} is noteworthy. The chemical shifts of the ring hydrogens in 6-substituted quinoxalines have been correlated with π -electron charge density, after correction for *N*-anisotropic and ring current effects.²⁵⁷

A study of the ^1H chemical shifts of 2,3,6-trimethylquinoxaline in carbon tetrachloride, trifluoroacetic acid, and fluorosulfonic acid indicated that the carbocyclic ring participates in the positive charge distribution to the extent of about 25–30% in the *mono*-protonated species and 15–20% in the *di*-protonated quinoxaline.²⁵⁸ 2,3-Diphenylquinoxaline forms a stable monocation in trifluoroacetic acid, as indicated by the downfield hydrogen signals in this solvent, compared to those in CH_2Cl_2 .²⁵⁹ The NMR spectra of quinoxaline 1-oxide, 1,4-dioxide²⁶⁰ and the *N*-oxides of 2- and 3-substituted quinoxalines have been reported.²⁶¹ Analysis of the chemical shift values of quinoxaline-2,3-dicarboxylic acids in dimethylformamide and carbon tetrachloride indicated the presence of an equilibrium between monomeric and dimeric species. In quinoxaline-2,3-dicarboxylic acid 1,4-dioxide no such equilibrium was observed, owing to the presence of intramolecular hydrogen bonding.²⁶²

The existence of the covalently hydrated quinoxaline **252** discussed above was further confirmed by NMR examination of the 1-methylquinoxalinium cation in basic methanol- d_4 . This proved to be complex,

²⁵⁵ P. J. Black and M. L. Heffernan, *Aust. J. Chem.* **18**, 707 (1965).

²⁵⁶ P. J. Brignell, A. R. Katritzky, R. E. Reavill, G. W. H. Cheeseman, and A. A. Sarsfield, *J. Chem. Soc.*, 1241 (1967).

²⁵⁷ (a) Y. Sasaki, M. Hatanaka, and M. Suzuki, *Yakugaku Zasshi* **89**, 64 (1969) [*CA* **70**, 96015 (1969)]; (b) Y. Sasaki and M. Suzuki, *Chem. Pharm. Bull.* **18**, 1774 (1970).

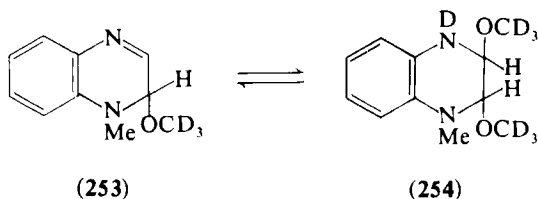
²⁵⁸ (a) R. Pastor and J. Musso, *Bull. Soc. Chim. Fr.*, 2339 (1972); (b) R. Pastor, J. Musso, and A. Cambon, *ibid.*, 3009 (1973).

²⁵⁹ D. J. Bleas and S. S. Danyluk, *Tetrahedron* **23**, 2927 (1967).

²⁶⁰ K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* **11**, 681 (1963).

²⁶¹ T. N. Ul'yanova, G. G. Dvoryantseva, Yu. N. Sheinker, A. S. Elina, and I. S. Musatova, *Khim. Geterotsikl. Soedin.*, 1115 (1973) [*CA* **79**, 125379 (1973)].

²⁶² L. L. Gordienko, Yu. S. Rozum, N. P. Romazanovich, and T. Ya. Lavrenyuk, *Khim. Geterotsikl. Soedin.*, 702 (1973) [*CA* **79**, 41702 (1973)].



and best interpreted by postulating the presence of the tetrahydroquinoxaline **254** in equilibrium with **253**.²⁵¹

Chemical shifts and coupling constants of substituted 1,2,3,4-tetrahydroquinoxalines indicate that the heterocyclic ring in these derivatives is in the half-chair form.²⁶³ The variation of the cis vicinal and geminal couplings resulting from acylation on nitrogen indicates that the acylated derivatives have a slightly flattened half-chair conformation.²⁶³

An examination of the H–F spin–spin coupling of 2-substituted-3-trifluoromethylquinoxalines and their mono- and di-*N*-oxides indicated that $J_{\text{H-F}}$ alters as the H–F internuclear distance varies. This effect is best explained by a “through-space” interaction.²⁶⁴

The ¹³C chemical shifts for quinoxalines have been explained in terms of the inductive and resonance effects of the substituents.²⁶⁵ Resonances at 144.8 and 142.8 δ in the spectrum of quinoxaline in deuteriochloroform are assigned to carbon atoms 2 and 3 and 9 and 10, respectively. Carbons 5 and 8 resonate at 129.6, and carbons 6 and 7 at 129.4.²⁶⁶

D. OTHER PHYSICAL PROPERTIES

The infrared spectra of quinoxaline mono- and di-*N*-oxides; 3-quinoxalinone 1-oxides, and 1-hydroxyquinoxaline 2,3-diones have been reported, and the ring stretching vibrations and C=O and N–O stretching frequencies were assigned.²⁶⁷ 2-Methyl-6-amino- and 2-methyl-6-nitro-1,2,3,4-tetrahydro-3-quinoxalinones have been examined

²⁶³ R. A. Aguilera, J. C. Duplan, and C. Nofre, *Bull. Soc. Chim. Fr.*, 4491 (1968).

²⁶⁴ E. Abushanab, *J. Am. Chem. Soc.* **93**, 6532 (1971).

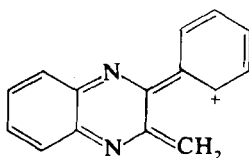
²⁶⁵ R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *J. Am. Chem. Soc.* **91**, 6381 (1969).

²⁶⁶ L. F. Johnson and W. C. Jankowski, “Carbon-13 N.M.R. Spectra.” Wiley (Interscience), New York, 1972.

²⁶⁷ M. K. A. Khan, M. J. Qureshi, and Y. Ahmad, *Pakistan J. Sci. Ind. Res.* **15**, 252 (1972) [*CA* **79**, 52426 (1973)].

in the infrared, both in KBr disks and in solution in carbon tetrachloride and carbon disulfide. The predominant tautomer was found to be the lactam form.²⁶⁸

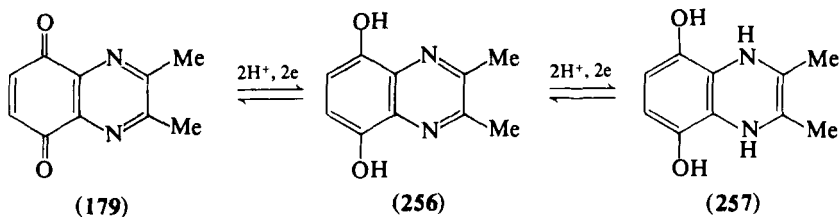
The mass spectra of a number of quinoxalines have been reported.^{269–271} The parent heterocycle shows fragment ions resulting from the loss of one and two molecules of HCN. Similarly in the case of 2-alkyl and 2-arylquinoxalines, $M - \text{HCN}$, and $M - \text{RCN}$ ions are observed. A notable feature of the spectrum of 2-methyl-3-phenylquinoxaline is the formation of an intense $(M-1)^+$ ion. This was shown by deuterium labeling to be the result of hydrogen migration from the methyl group to the phenyl ring, followed by expulsion of a hydrogen atom to give the cation **255**.^{270, 271}



(255)

The M-17 peak with the expected metastable ion was found to be a significant feature of the mass spectra of all substituted mono-*N*-oxides examined and is assigned to a one-step elimination of the hydroxyl radical. For quinoxaline dioxides the M-16 peak is more important and is due to the preferential loss of an oxygen atom from the molecular ion.²⁶⁹

Polarographic studies have been carried out on quinoxalines,^{272–274}



²⁶⁸ J. Klicnar, P. Vetesnik, and Z. Cimpr, *Sb. Ved. Pr., Vys. Sk. Chemickotechnol., Pardubice* **18**, 5 (1968) [*CA* **72**, 66890 (1970)].

²⁶⁹ H. Yoshizumi, E. Hayashi, and H. Nakata, *Tetrahedron Lett.*, 2985 (1967).

²⁷⁰ S. N. Bannore, J. L. Bose, K. G. Das, and V. N. Gogte, *Indian J. Chem.* **7**, 654 (1969).

²⁷¹ (a) A. Karjalainen and H. Kreiger, *Suom. Kemistil. B* **43**, 273 (1970); (b) V. Kovacic, M. Fedoronko, and I. Jezo, *Org. Mass. Spectrom.* **7**, 449 (1973).

²⁷² L. L. Gordienko, Yu. S. Rozum, A. G. Chukhlantseva, and V. N. Rudenko, *Teor. Eksp. Khim.* **5**, 840 (1969) [*CA* **72**, 99718 (1970)].

²⁷³ R. Kuhn, P. Skrabal and P. H. H. Fisher, *Tetrahedron* **24**, 1843 (1968).

²⁷⁴ M. Takagi, R. Hosogaki, and S. Ono, *Rev. Polarography* **14**, 367 (1967).

quinoxaline *N*-oxides,²⁷⁵ and 2,3-dimethylquinoxaline-5,8-dione (**179**).²⁷⁶ The reduction wave of the quinoxaline ring shows reversibility, but that of the N—O group is irreversible.²⁷⁵ The polarographic reduction of **179** was found to be a composite of the known reduction mechanism of quinones and quinoxalines,²⁷⁶ resulting in first hydroquinone (**256**) and then 1,4-dihydroquinoxaline (**257**) formation.

²⁷⁵ Y. Kidani, K. Ohira, and H. Koike, *Yakugaku Zasshi* **93**, 157 (1968) [*CA* **78**, 135349 (1973)].

²⁷⁶ W. F. Gum and M. M. Joullié, *J. Org. Chem.* **32**, 53 (1967).

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